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(54) Title: A METHOD OF TREATING CANCER

(57) Abstract

The instant invention provides for a method of inhibiting prenyl–protein transferases and treating cancer which comprises administering to a mammal a prenyl–protein transferase inhibitor which is an inhibitor of cellular processing of the H–Ras and K4B–Ras proteins. The invention also provides for a method of inhibiting farnesyl–protein transferase and geranylgeranyl–protein transferase type I by administering a compound that is a dual inhibitor of both of those prenyl–protein transferases. A method of identifying a prenyl–protein transferase inhibitor which is an inhibit or of *in vivo* growth of cancer cells is also disclosed. The instant method comprises a cell-based *in vitro* assay which determines the physical state of a protein substrate of geranylgeranyl–protein transferase type I.

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TITLE OF THE INVENTION

A METHOD OF TREATING CANCER

BACKGROUND OF THE INVENTION

The present invention relates to methods of inhibiting prenyl-protein transferases and treating cancer which utilize prenyl-protein transferase inhibitors which inhibit the cellular processing of both the H-Ras protein and the K4B-Ras protein. The present invention also relates to a method of identifying such compounds.

Prenylation of proteins by intermediates of the isoprenoid biosynthetic pathway represents a class of post-translational modification (Glomset, J. A., Gelb, M. H., and Farnsworth, C. C. (1990), Trends Biochem. Sci. 15, 139-142; Maltese, W. A. (1990), FASEB J. 4, 3319-3328). This modification typically is required for the membrane localization and function of these proteins. Prenylated proteins share characteristic C-terminal sequences including CAAX (C, Cys; A, usually aliphatic amino acid; X, another amino acid), XXCC, or XCXC. Three post-translational processing steps have been described for proteins having a C-terminal CAAX sequence: addition of either a 15 carbon (farnesyl) or 20 carbon (geranylgeranyl) isoprenoid to the Cys residue, proteolytic cleavage of the last 3 amino acids, and methylation of the new C-terminal carboxylate (Cox, A. D. and Der, C. J. (1992a), *Critical Rev. Oncogenesis* 3:365-400; Newman, C. M. H. and Magee, A. I. (1993), *Biochim. Biophys. Acta* 1155:79-96). Some proteins may also have a fourth modification: palmitoylation of one or two Cys residues N-terminal to the farnesylated Cys. While some mammalian cell proteins terminating in XCXC are carboxymethylated, it is not clear whether carboxy methylation follows prenylation of proteins terminating with a XXCC motif (Clarke, S. (1992), Annu. Rev. Biochem. 61, 355-386). For all of the prenylated proteins, addition of the isoprenoid is the first step and is required for the subsequent steps (Cox, A. D. and Der, C. J.

(1992a), *Critical Rev. Oncogenesis* 3:365-400; Cox, A. D. and Der, C. J. (1992b) *Current Opinion Cell Biol.* 4:1008-1016).

Three enzymes have been described that catalyze protein prenylation: farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGTase-I), and geranylgeranyl-protein transferase type-II (GGTase-II, also called Rab GGTase). These enzymes are found in both yeast and mammalian cells (Clarke, 1992; Schafer, W. R. and Rine, J. (1992) *Annu. Rev. Genet.* 30:209-237). Each of these enzymes selectively uses farnesyl diphosphate or geranylgeranyl diphosphate as the isoprenoid donor and selectively recognizes the protein substrate. FPTase farnesylates CAAX-containing proteins that end with Ser, Met, Cys, Gln or Ala. For FPTase, CAAX tetrapeptides comprise the minimum region required for interaction of the protein substrate with the enzyme. The enzymological characterization of these three enzymes has demonstrated that it is possible to selectively inhibit one with little inhibitory effect on the others (Moores, S. L., Schaber, M. D., Mosser, S. D., Rands, E., O'Hara, M. B., Garsky, V. M., Marshall, M. S., Pompliano, D. L., and Gibbs, J. B., *J. Biol. Chem.*, 266:17438 (1991), U.S. Pat. No. 5,470,832).

The prenylation reactions have been shown genetically to be essential for the function of a variety of proteins (Clarke, 1992; Cox and Der, 1992a; Gibbs, J. B. (1991), *Cell* 65: 1-4; Newman and Magee, 1993; Schafer and Rine, 1992). This requirement often is demonstrated by mutating the CAAX Cys acceptors so that the proteins can no longer be prenylated. The resulting proteins are devoid of their central biological activity. These studies provide a genetic "proof of principle" indicating that inhibitors of prenylation can alter the physiological responses regulated by prenylated proteins.

The Ras protein is part of a signaling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation. Biological and biochemical studies of Ras action indicate that Ras functions like a G-regulatory protein. In the

inactive state, Ras is bound to GDP. Upon growth factor receptor activation, Ras is induced to exchange GDP for GTP and undergoes a conformational change. The GTP-bound form of Ras propagates the growth stimulatory signal until the signal is terminated by the intrinsic GTPase activity of Ras, which returns the protein to its inactive GDP bound form (D.R. Lowy and D.M. Willumsen, *Ann. Rev. Biochem.* *62*:851-891 (1993)). Activation of Ras leads to activation of multiple intracellular signal transduction pathways, including the MAP Kinase pathway and the Rho/Rac pathway (Joneson *et al.*, Science *271*:810-812).

Mutated *ras* genes are found in many human cancers, including colorectal carcinoma, exocrine pancreatic carcinoma, and myeloid leukemias. The protein products of these genes are defective in their GTPase activity and constitutively transmit a growth stimulatory signal.

The Ras protein is one of several proteins that are known to undergo post-translational modification. Farnesyl-protein transferase utilizes farnesyl pyrophosphate to covalently modify the Cys thiol group of the Ras CAAX box with a farnesyl group (Reiss *et al., Cell, 62*:81-88 (1990); Schaber *et al., J. Biol. Chem., 265*:14701-14704 (1990); Schafer *et al., Science, 249*:1133-1139 (1990); Manne *et al., Proc. Natl. Acad. Sci USA, 87*:7541-7545 (1990)).

Ras must be localized to the plasma membrane for both normal and oncogenic functions. At least 3 post-translational modifications are involved with Ras membrane localization, and all 3 modifications occur at the C-terminus of Ras. The Ras C-terminus contains a sequence motif termed a "CAAX" or "Cys-Aaa-Aaa-Xaa" box (Cys is cysteine, Aaa is an aliphatic amino acid, the Xaa is any amino acid) (Willumsen *et al., Nature 310*:583-586 (1984)). Depending on the specific sequence, this motif serves as a signal sequence for the enzymes farnesyl-protein transferase or geranylgeranyl-protein transferase, which catalyze the alkylation

of the cysteine residue of the CAAX motif with a C_{15} or C_{20} isoprenoid, respectively. (S. Clarke., *Ann. Rev. Biochem. 61*:355-386 (1992); W.R. Schafer and J. Rine, *Ann. Rev. Genetics 30*:209-237 (1992)).

Other farnesylated proteins include the Ras-related GTP-binding proteins such as RhoB, fungal mating factors, the nuclear lamins, and the gamma subunit of transducin. James, et al., *J. Biol. Chem. 269*, 14182 (1994) have identified a peroxisome associated protein Pxf which is also farnesylated. James, et al., have also suggested that there are farnesylated proteins of unknown structure and function in addition to those listed above.

Inhibitors of farnesyl-protein transferase (FPTase) have been described in two general classes. The first class includes analogs of farnesyl diphosphate (FPP), while the second is related to protein substrates (e.g., Ras) for the enzyme. The peptide derived inhibitors that have been described are generally cysteine containing molecules that are related to the CAAX motif that is the signal for protein prenylation. (Schaber *et al., ibid*; Reiss *et. al., ibid*; Reiss *et al., PNAS, 88*:732-736 (1991)). Such inhibitors may inhibit protein prenylation while serving as alternate substrates for the farnesyl-protein transferase enzyme, or may be purely competitive inhibitors (U.S. Patent 5,141,851, University of Texas; N.E. Kohl *et al., Science, 260*:1934-1937 (1993); Graham, et al., *J. Med. Chem., 37*, 725 (1994)).

Mammalian cells express four types of Ras proteins (H-, N-, K4A-, and K4B-Ras) among which K4B-Ras is the most frequently mutated form of Ras in human cancers. The genes that encode these proteins are abbreviated H-*ras*, N-*ras* , K4A-*ras* and K4B-*ras* respectively. H-*ras* is an abbreviation for Harvey-ras. K4A-*ras* and K4B-*ras* are abbreviations for the Kirsten splice variants of *ras* that contain the 4A and 4B exons, respectively. Inhibition of farnesyl-protein transferase has been shown to block the growth of H-*ras*-transformed cells in soft agar and to modify other aspects of

their transformed phenotype. It has also been demonstrated that certain inhibitors of farnesyl-protein transferase selectively block the processing of the H-Ras oncoprotein intracellularly (N.E. Kohl *et al.*, *Science*, *260*:1934-1937 (1993) and G.L. James *et al.*, *Science*, *260*:1937-1942 (1993). Recently, it has been shown that an inhibitor of farnesyl-protein transferase blocks the growth of H-*ras*-dependent tumors in nude mice (N.E. Kohl *et al.*, *Proc. Natl. Acad. Sci U.S.A.*, *91*:9141-9145 (1994) and induces regression of mammary and salivary carcinomas in H-*ras* transgenic mice (N.E. Kohl *et al.*, *Nature Medicine*, 1:792-797 (1995).

Indirect inhibition of farnesyl-protein transferase *in vivo* has been demonstrated with lovastatin (Merck & Co., Rahway, NJ) and compactin (Hancock *et al.*, *ibid*; Casey *et al.*, *ibid*; Schafer *et al.*, *Science 245*:379 (1989)). These drugs inhibit HMG-CoA reductase, the rate limiting enzyme for the production of polyisoprenoids including farnesyl pyrophosphate. Inhibition of farnesyl pyrophosphate biosynthesis by inhibiting HMG-CoA reductase blocks Ras membrane localization in cultured cells.

It has been disclosed that the lysine-rich region and terminal CVIM sequence of the C-terminus of K4B-Ras confer resistance to inhibition of the cellular processing of that protein by certain selective FPTase inhibitors. (James, et al., *J. Biol. Chem. 270*, 6221 (1995)) Those FPTase inhibitors were effective in inhibiting the processing of H-Ras proteins. James et al., suggested that prenylation of the K4B-Ras protein by GGTase contributed to the resistance to the selective FPTase inhibitors. (Zhang et al, *J. Biol. Chem. 272* :10232-239 (1997); Rowell et al, *J. Biol. Chem. 272* :14093-14097 (1997); Whyte et al, *J. Biol. Chem. 272* :14459-14464 (1997)).

Several groups of scientists have recently disclosed compounds that are non-selective FPTase/GGTase inhibitors. (Nagasu et al. *Cancer Research, 55*:5310-5314 (1995); PCT application WO 95/25086).

It is the object of the instant invention to provide a method for inhibiting prenyl-protein transferase which utilizes an inhibitor of cellular processing of the H-Ras and K4B-Ras proteins.

It is the object of the instant invention to provide a method for identifying a prenyl-protein transferase inhibitor which is an inhibitor of cellular processing of the H-Ras and K4B-Ras proteins.

It is also the object of the present invention to provide compounds that are prenyl-protein transferase inhibitors and which inhibit cellular processing of the H-Ras and K4B-Ras proteins.

A composition which comprises such an inhibitor compound is used in the present invention to treat cancer.

SUMMARY OF THE INVENTION

The instant invention provides for a method of inhibiting prenyl-protein transferases and treating cancer which comprises administering to a mammal a prenyl-protein transferase inhibitor which is an inhibitor of cellular processing of the H-Ras and K4B-Ras proteins. The invention also provides for a method of inhibiting farnesyl-protein transferase and geranylgeranyl-protein transferase type I by administering a compound that is a dual inhibitor of both of those prenyl-protein transferases. A method of identifying a prenyl-protein transferase inhibitor which is an inhibitor of *in vivo* growth of cancer cells is also disclosed. The instant method comprises a cell-based *in vitro* assay which determines the physical state of a protein substrate of geranylgeranyl-protein transferase type I.

BRIEF DESCRIPTION OF THE FIGURES

FIGURE 1: *SDS-PAGE Electrophoresis of PSN-1 cell lysates:*

The figure shows an X-ray film that was exposed to the SDS-PAGE electrophoresis gel of radio-labeled K4B-Ras proteins that have been purified by double immunoprecipitation. The proteins were isolated from the lysates of PSN-1 cells that had been exposed to vehicle, 10 μM lovastatin or 10 μM Compound 1 for

the length of time indicated. Details of the assay procedure can be found in Example 15.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a method of inhibiting prenyl-protein transferase which comprises administering to a mammal in need thereof a pharmaceutically effective amount of a compound which has certain characteristics that are indicative of *in vivo* efficacy as an inhibitor of the growth of cancer cells.

Preferably, the prenyl-protein transferases that are being inhibited by the instant method are both farnesyl-protein transferase and geranylgeranyl-protein transferase type I. Preferably the compound that is being administered is a dual inhibitor of farnesyl-protein transferase and geranylgeranyl-protein transferase type I.

The present invention further relates to a method of identifying a compound which is efficacious *in vivo* as an inhibitor of cancer cell growth. The instant method comprises a cell-based *in vitro* assay which determines the physical state of a protein that is a substrate of geranylgeranyl-protein transferase Type I and/or farnesyl-protein transferase (whether or not the protein has been processed). The ability of the prenyl-protein transferase inhibitor to inhibit the processing of newly synthesized protein substrate is indicative of *in vivo* efficacy as an inhibitor of the growth of cancer cells.

A compound which is anticipated to inhibit the cellular processing of K4B-Ras protein based on the assays described herein will also inhibit the cellular processing of H-Ras protein.

In an embodiment of the assay utilized in the instant method, which is referred to as the Processing Assay, the assay comprises the steps of:

a) incubating the cells in the presence of test compound;

b) isolating a protein that is a substrate of one or both of geranylgeranyl-protein transferase Type I and farnesyl-protein transferase; and

c) measuring the amount of the protein that has been processed and the amount of protein that has not been processed.

Preferably, the protein of step b) in the Processing Assay is a substrate of both geranylgeranyl-protein transferase Type I and farnesyl-protein transferase. Most preferably, the protein of step b) is K4B-Ras.

In another embodiment of the assay utilized in the instant invention, which is referred to as the Alternative Processing Assay, the assay comprises the steps of:

a) incubating test cells in the presence of a test compound in an incubation medium;

b) isolating a protein that is a substrate of one or both of geranylgeranyl-protein transferase Type I and farnesyl-protein transferase; and

c) measuring the amount of the protein that has not been processed.

Preferably, the protein of step b) in the Alternative Processing Assay is a substrate of geranylgeranyl-protein transferase Type I. Most preferably, the protein of step b) is Rap1.

Preferably, in step b) of the Alternative Processing Assay the step of isolating the proteins comprises the additional steps of lysing the cells and then separating cellular proteins by electrophoresis. More preferably, the step of isolating the proteins further comprises the additional steps of performing a Western blot on the electrophoretic gel using an antibody specific for the unprocessed protein. Preferably, the antibody specific for the unprocessed protein is anti-Rap1a antibody (Santa Cruz Biochemical SC1482).

It is preferable that the compound identified by the instant method is an inhibitor of farnesyl-protein transferase and/or geranylgeranyl protein transferase type I. Therefore, the instant method of identifying a compound may further comprise one or both of the steps of:

d) assessing a test compound for its *in vitro* inhibitory activity

against transfer of a geranylgeranyl residue to a protein or peptide substrate comprising a $CAAX^G$ motif by geranylgeranyl-protein transferase type I in the presence of a modulating anion;

e) assessing a test compound for its *in vitro* inhibitory activity against transfer of a farnesyl residue to a protein or peptide substrate comprising a $CAAX^F$ motif by farnesyl-protein transferase.

The term "$CAAX^G$" will refer to such motifs that may be geranylgeranylated by GGTase-I. In particular, such "$CAAX^G$" motifs include (the corresponding human protein is in parentheses): CVIM (K4B-Ras) (SEQ.ID.: 1), CVLL (mutated H-Ras) (SEQ.ID.: 2), CVVM (N-Ras) (SEQ.ID.: 3), CIIM (K4A-Ras) (SEQ.ID.: 4), CLLL (Rap-IA) (SEQ.ID.: 5), CQLL (Rap-IB) (SEQ.ID.: 6), CSIM (SEQ.ID.: 7), CAIM (SEQ.ID.: 8), CKVL (SEQ.ID.: 9), CLIM (PFX) (SEQ.ID.: 10) and CVIL (Rap2B) (SEQ.ID.: 12). Preferably, the CAAX motif is CVIM (SEQ.ID.: 1). It is understood that some of the "$CAAX^G$" containing protein or peptide substrates may also be farnesylated by farnesyl-protein transferase.

As used herein, the term "$CAAX^F$" is used to designate a protein or peptide substrate that incorporates four amino acid C-terminus motif that is farnesylated by farnesyl-protein transferase. In particular, such "$CAAX^F$" motifs include (the corresponding human protein is in parentheses): CVLS (H-ras) (SEQ.ID.: 11), CVIM (K4B-Ras) (SEQ.ID.: 1), CVVM (N-Ras) (SEQ.ID.: 3) and CNIQ (Rap2A) (SEQ.ID.: 13). It is understood that certain of the "$CAAX^F$" containing protein or peptide substrates may also be geranylgeranylated by GGTase-I.

It is contemplated that any cell line can be used in connection with the instant assay. Examples include 3T3, C33a, PSN-1 (a human pancreatic carcinoma cell line) and K-*ras*-transformed Rat-1 cells. Preferred cell lines for use in the instant assay has been found to be PSN-1 and K-*ras*-transformed Rat-1 cells.

The assay medium used in the instant assay may be selected from any medium useful for maintaining cell viability, provided that the media is depleted of cysteine and methionine. Preferably the assay medium comprises methionine-free RPMI or cysteine-free/methionine-free DMEM. Most preferably the assay medium is selected from methionine-free RPMI supplemented with 2% fetal bovine serum; and cysteine-free/methionine-free DMEM supplemented with 0.035 ml of 200 mM glutamine (Gibco), 2% fetal bovine serum

Preferably the protein of step b) in the Processing Assay that is a substrate of one or both of geranylgeranyl-protein transferase type I and farnesyl-protein transferase is isolated by the additional steps of lysing the cells and then immunoprecipitating the proteins from the lysate. Preferably the supernatant from the lysate is immunoprecipitated twice.

Most preferably, when the protein of step b) in the Processing Assay is K4B-Ras, the mixture of processed and unprocessed K4B-Ras proteins undergo a first immunoprecipitation with a pan Ras monoclonal antibody, such as Y13-259 (Calbiochem) and a second immunoprecipitation with a K-Ras specific monoclonal antibody, such as c-K-ras Ab-1 (Calbiochem).

Preferably, when the protein of step b) in the Processing Assay is Rap1, the mixture of processed and unprocessed Rap1 proteins undergo two separate immunoprecipitation steps with a Rap1 antibody, such as Rap1/Krev1 (Santa Cruz Biotech).

There are many methods known to one of ordinary skill in the art for distinguishing and measuring the relative amounts of processed and unprocessed protein in the lysate after it has been isolated. Preferably, the method utilized for separating the processed and unprocessed protein is subjecting a mixture of proteins to SDS-PAGE on a 12% acrylamide gel and then visualizing the protein.

There are further many methods known in the art for visualizing the separated processed and unprocessed proteins. For example, the proteins themselves may be radiolabeled and

the proteins then visualized by fluorography. A method of radio-labeling the proteins is by introducing radiolabeled amino acids to the incubation medium. Preferably, the radiolabeled amino acids are added to the assay medium in the presence of the test compound. Such a method of radiolabeling a protein provides for assessment of the processing status of only newly synthesized protein.

The SDS-PAGE gel may also be subjected to western blot procedures. An antibody to the proteins may be used to mark the separated processed and unprocessed protein through radio-labeling of the antibody; or the location of that antibody may be visualized by interaction with a second labeled antibody or an second antibody that generates a fluorescent marker.

Preferably, when the protein of step b) in the Processing Assay is Rap1A, the mixture of processed and unprocessed Rap1A proteins is separated by electrophoresis and then visualized by a Western blot that is performed using an antibody which is specific for the unprocessed species of Rap1A.

It is further preferred that the compound identified by the instant method is also a potent in vivo farnesyl-protein transferase inhibitor. It has been surprisingly found that such a potent dual inhibitor is particularly useful as an in vivo inhibitor of the growth of cancer cells, particularly those cancers characterized by a mutated K4B-Ras protein, at concentrations of inhibitor that do not cause mechanism based toxicity. Mechanism-based toxicity of farnesyl-protein transferase inhibitors can be anticipated in rapidly proliferating tissues, for example, the bone marrow.

The inhibitor compounds identified by the instant method are useful in the inhibition of prenyl-protein transferase and the treatment of cancer and other proliferative disorders in mammals in need thereof. Preferably the compounds of the invention inhibit the processing of greater than (>) 25% of the newly synthesized protein that is a substrate of an enzyme that can modify the K4B-Ras protein C-terminus after incubation of the assay cells with the compound of the invention. More preferably the compounds of

the invention inhibit the processing of greater than (>) 50% of the newly synthesized protein that is a substrate of an enzyme that can modify the K4B-Ras protein C-terminus after incubation. The preferred time of incubation for determining the percentage of inhibition of processing is from about 2 hours to about 24 hours. More preferably, the time of incubation is from about 4 hours to about 8 hours. Preferably, the enzyme that can modify the K4B-Ras protein C-terminus is selected from farnesyl-protein transferase and geranylgeranyl-protein transferase type I.

Preferably, such an inhibitor is further characterized by one or both of:

a) an IC_{50} (a measurement of *in vitro* inhibitory activity) of less than about 5 μM against transfer of a geranylgeranyl residue to a protein or peptide substrate comprising a $CAAX^G$ motif by geranylgeranyl-protein transferase type I in the presence of a modulating anion, and
b) an IC_{50} (a measurement of *in vitro* inhibitory activity) of less than about 1 μM against transfer of a farnesyl residue to a protein or peptide substrate comprising a $CAAX^F$ motif by farnesyl-protein transferase.

More preferably, such an inhibitor is further characterized by one or both of:

c) an IC_{50} (a measurement of *in vitro* inhibitory activity) of less than about 1 μM against transfer of a geranylgeranyl residue to a protein or peptide substrate comprising a $CAAX^G$ motif by geranylgeranyl-protein transferase type I in the presence of a modulating anion, and
d) an IC_{50} (a measurement of *in vitro* inhibitory activity) of less than about 500 nM against transfer of a farnesyl residue to a protein or peptide substrate comprising a $CAAX^F$ motif by farnesyl-protein transferase.

The modulating anion may be selected from any type of molecule containing an anion moiety. Preferably the modulating anion is selected from a phosphate or sulfate containing anion.

Particular examples of modulating anions useful in the instant GGTase-I inhibition assay include adenosine 5'-triphosphate (ATP), 2'-deoxyadenosine 5'-triphosphate (dATP), 2'-deoxycytosine 5'-triphosphate (dCTP), β-glycerol phosphate, pyrophosphate, guanosine 5'-triphosphate (GTP), 2'-deoxyguanosine 5'-triphosphate (dGTP), uridine 5'-triphosphate, dithiophosphate, 3'-deoxythymidine 5'-triphosphate, tripolyphosphate, D-myo-inositol 1,4,5-triphosphate, chloride, guanosine 5'-monophosphate, 2'-deoxyguanosine 5'-monophosphate, orthophosphate, formycin A, inosine diphosphate, trimetaphosphate, sulfate and the like. Preferably, the modulating anion is selected from adenosine 5'-triphosphate, 2'-deoxyadenosine 5'-triphosphate, 2'-deoxycytosine 5'-triphosphate, β-glycerol phosphate, pyrophosphate, guanosine 5'-triphosphate, 2'-deoxyguanosine 5'-triphosphate, uridine 5'-triphosphate, dithiophosphate, 3'-deoxythymidine 5'-triphosphate, tripolyphosphate, D-myo-inositol 1,4,5-triphosphate and sulfate. Most preferably, the modulating anion is selected from adenosine 5'-triphosphate, β-glycerol phosphate, pyrophosphate, dithiophosphate and sulfate.

The term prenyl-protein transferase inhibiting compound refers to compounds which antagonize, inhibit or counter-act the activity of the genes coding farnesyl-protein transferase and/or geranylgeranyl-protein transferase or the proteins produced in response thereto. In the instant method, >25% inhibition of the processing of the K4B-Ras protein by a test compound indicates that the test compound is an inhibitor of an enzyme that can modify the C-terminus of the K4B-Ras protein.

When a particular Ras protein is referred to herein by a term such as "K4B-Ras", "N-Ras", "H-Ras" and the like, such a term represents both the protein arising from expression of the corresponding wild type *ras* gene and various proteins arising from expression of *ras* genes containing various point mutations. When a particular *ras* gene is referred to herein by a term such as "K4B-*ras*", "N-*ras*", "H-*ras*" and the like, such a term represents both the wild type *ras* gene and *ras* genes containing various point mutations.

The term selective as used herein refers to the inhibitory activity of the particular compound against one biological activity (for instance, inhibition of prenyl-protein transferase) when compared to the inhibitory activity of the compound against another biological activity. It is understood that the greater the selectivity of a prenyl-protein transferase inhibitor, the more preferred such a compound is for the methods of treatment described.

The preferred therapeutic effect provided by the instant composition is the treatment of cancer and specifically the inhibition of cancerous tumor growth and/or the regression of cancerous tumors. Cancers which are treatable in accordance with the invention described herein include cancers of the brain, breast, colon, genitourinary tract, prostate, skin, lymphatic system, pancreas, rectum, stomach, larynx, liver and lung. More particularly, such cancers include histiocytic lymphoma, lung adenocarcinoma, pancreatic carcinoma, colo-rectal carcinoma, small cell lung cancers, bladder cancers, head and neck cancers, acute and chronic leukemias, melanomas, and neurological tumors.

The composition of this invention is also useful for inhibiting other proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes (i.e., the Ras gene itself is not activated by mutation to an oncogenic form) with said inhibition being accomplished by the administration of an effective amount of the instant composition to a mammal in need of such treatment. For example, the composition is useful in the treatment of neurofibromatosis, which is a benign proliferative disorder.

The compound of the instant invention is also useful in the prevention of restenosis after percutaneous transluminal coronary angioplasty by inhibiting neointimal formation (C. Indolfi et al. *Nature medicine*, 1:541-545(1995).

The instant compound may also be useful in the treatment and prevention of polycystic kidney disease (D.L.

Schaffner et al. *American Journal of Pathology*, 142:1051-1060 (1993) and B. Cowley, Jr. et al. *FASEB Journal*, 2:A3160 (1988)).

The instant compounds may also inhibit tumor angiogenesis, thereby affecting the growth of tumors (J. Rak et al. *Cancer Research*, 55:4575-4580 (1995)). Such anti-angiogenesis properties of the instant compounds may also be useful in the treatment of certain forms of vision deficit related to retinal vascularization.

The instant compounds may also be useful in the treatment of certain viral infections, in particular in the treatment of hepatitis delta and related viruses (J.S. Glenn et al. *Science*, 256:1331-1333 (1992).

The instant compounds may also be useful as inhibitors of proliferation of vascular smooth muscle cells and therefore useful in the prevention and therapy of arteriosclerosis and diabetic vascular pathologies.

The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets.

These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropylmethyl-cellulose or hydroxypropylcellulose, or a time delay material such as ethyl cellulose, cellulose acetate buryrate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethyleneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more

preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring agents, preservatives and antioxidants.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous solutions. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulation.

The injectable solutions or microemulsions may be introduced into a patient's blood-stream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400 intravenous pump.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of Formula A may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at

the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula A are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specific amounts, as well as any product which results, directly or indirectly, from combination of the specific ingredients in the specified amounts.

The compounds identified by the instant method may also be co-administered with other well known therapeutic agents that are selected for their particular usefulness against the condition that is being treated. For example, the instant compounds may be useful in combination with known anti-cancer and cytotoxic agents. Similarly, the instant compounds may be useful in combination with agents that are effective in the treatment and prevention of neurofibromatosis, restinosis, polycystic kidney disease, infections of hepatitis delta and related viruses and fungal infections. The instant compounds may also be useful in combination with other inhibitors of parts of the signaling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation. Thus, the instant compounds may be utilized in combination with farnesyl pyrophosphate competitive inhibitors of the activity of farnesyl-protein transferase or in combination with a compound which has

Raf antagonist activity. The instant compounds may also be co-administered with compounds that are selective inhibitors of geranylgeranyl protein transferase or selective inhibitors of farnesyl-protein transferase.

The compounds of the instant invention may also be co-administered with other well known cancer therapeutic agents that are selected for their particular usefulness against the condition that is being treated. Included in such combinations of therapeutic agents are combinations of the instant prenyl-protein transferase inhibitors and an antineoplastic agent. It is also understood that the instant combination of antineoplastic agent and inhibitor of prenyl-protein transferase may be used in conjunction with other methods of treating cancer and/or tumors, including radiation therapy and surgery.

If formulated as a fixed dose, such combination products employ the combinations of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its approved dosage range. Combinations of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a multiple combination formulation is inappropriate.

Radiation therapy, including x-rays or gamma rays which are delivered from either an externally applied beam or by implantation of tiny radioactive sources, may also be used in combination with an inhibitor of prenyl-protein transferase alone to treat cancer.

Additionally, compounds of the instant invention may also be useful as radiation sensitizers, as described in WO 97/38697, published on October 23, 1997, and herein incorporated by reference.

The instant compounds may also be useful in combination with other inhibitors of parts of the signaling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation. Thus, the instant compounds may be utilized in combination with farnesyl pyrophosphate competitive inhibitors of

the activity of farnesyl-protein transferase or in combination with a compound which has Raf antagonist activity.

The instant compounds may also be useful in combination with an integrin antagonist for the treatment of cancer, as described in U.S. Ser. No. 09/055,487, filed April 6, 1998, which is incorporated herein by reference.

As used herein the term an integrin antagonist refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to an integrin(s) that is involved in the regulation of angiogenisis, or in the growth and invasiveness of tumor cells. In particular, the term refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha v\beta 3$ integrin, which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha v\beta 5$ integrin, which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha v\beta 3$ integrin and the $\alpha v\beta 5$ integrin, or which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha v\beta 6$, $\alpha v\beta 8$, $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 5\beta 1$, $\alpha 6\beta 1$ and $\alpha 6\beta 4$ integrins. The term also refers to antagonists of any combination of $\alpha v\beta 3$, $\alpha v\beta 5$, $\alpha v\beta 6$, $\alpha v\beta 8$, $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 5\beta 1$, $\alpha 6\beta 1$ and $\alpha 6\beta 4$ integrins. The instant compounds may also be useful with other agents that inhibit angiogenisis and thereby inhibit the growth and invasiveness of tumor cells, including, but not limited to angiostatin and endostatin.

When a composition according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of a prenyl-protein transferase inhibitor are administered to a mammal undergoing treatment for cancer. Administration occurs in an amount of each type of inhibitor of between about 0.1 mg/kg of body weight

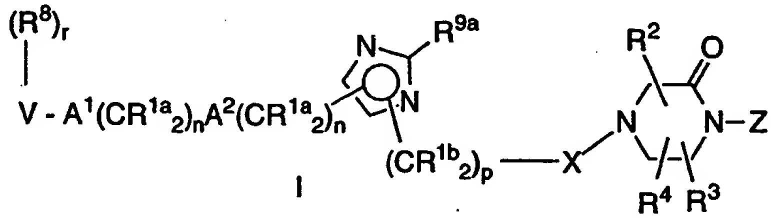
to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day. A particular therapeutic dosage that comprises the instant composition includes from about 0.01mg to about 1000mg of a prenyl-protein transferase inhibitor. Preferably, the dosage comprises from about 1mg to about 1000mg of a prenyl-protein transferase inhibitor.

Examples of an antineoplastic agent include, in general, microtubule-stabilising agents (such as paclitaxel (also known as Taxol®), docetaxel (also known as Taxotere®), or their derivatives); alkylating agents, anti-metabolites; epidophyllotoxin; an antineoplastic enzyme; a topoisomerase inhibitor; procarbazine; mitoxantrone; platinum coordination complexes; biological response modifiers and growth inhibitors; hormonal/anti-hormonal therapeutic agents and haematopoietic growth factors.

Example classes of antineoplastic agents include, for example, the anthracycline family of drugs, the vinca drugs, the mitomycins, the bleomycins, the cytotoxic nucleosides, the taxanes, the epothilones, discodermolide, the pteridine family of drugs, diynenes and the podophyllotoxins. Particularly useful members of those classes include, for example, doxorubicin, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, dichloro-methotrexate, mitomycin C, porfiromycin, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytosine arabinoside, podophyllotoxin or podo-phyllotoxin derivatives such as etoposide, etoposide phosphate or teniposide, melphalan, vinblastine, vincristine, leurosidine, vindesine, leurosine, paclitaxel and the like. Other useful antineoplastic agents include estramustine, cisplatin, carboplatin, cyclophosphamide, bleomycin, gemcitibine, ifosamide, melphalan, hexamethyl melamine, thiotepa, cytarabin, idatrexate, trimetrexate, dacarbazine, L-asparaginase, camptothecin, CPT-11, topotecan, ara-C, bicalutamide, flutamide, leuprolide, pyridobenzoindole derivatives, interferons and interleukins.

Compounds of the instant invention that are identified by the properties described hereinabove include:

(a) a compound represented by formula I:



I

wherein:

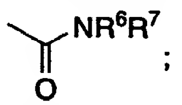
R^{1a} is selected from: hydrogen or C_1-C_6 alkyl;

R^{1b} is independently selected from:

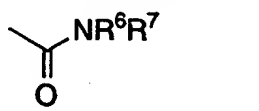
a) hydrogen,
b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, $-N(R^{10})_2$ or C_2-C_6 alkenyl,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or $-N(R^{10})_2$;

R^3 and R^4 selected from H and CH_3;

R^2 is selected from H; unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl,


;

or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,
2) heterocycle,
3) OR^6,
4) SR^{6a}, SO_2R^{6a}, or
5)  ;

and R^2 and R^3 are optionally attached to the same carbon atom;

R^6 and R^7 are independently selected from:

H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) halogen,
c) perfluoro-C_{1-4} alkyl, or
d) aryl or heterocycle;

R^{6a} is selected from:

C_{1-4} alkyl or C_{3-6} cycloalkyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^8 is independently selected from:

a) hydrogen,
b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} is hydrogen or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, O, -N(R^{10})-, or S(O)$_m$;

V is selected from:

a) hydrogen,

b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is S(O)$_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is S(O)$_m$;

X is -CH$_2$- or -C(=O)-;

Z is selected from:

1) a unsubstituted or substituted group selected from aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl, heteroarylsulfonyl, wherein the substituted group is substituted with one or more of the following:

a) C_{1-4} alkyl, unsubstituted or substituted with: C_{1-4} alkoxy, NR^{6}R^7, C_{3-6} cycloalkyl, unsubstituted or substituted aryl, heterocycle, HO, -S(O)$_m$R^{6a}, or -C(O)NR^{6}R^7,

b) aryl or heterocycle,

c) halogen,

d) OR^6,

e) NR^{6}R^7,

f) CN,

g) NO_2,

h) CF_3;

i) -S(O)$_m$R^{6a},

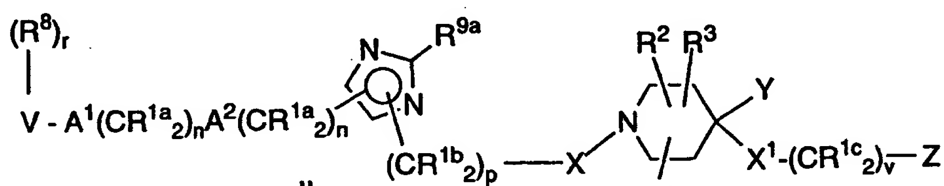
j) $-C(O)NR^6R^7$, or
k) C_3-C_6 cycloalkyl; or

2) unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_3-C_6 cycloalkyl or substituted C_3-C_6 cycloalkyl, wherein the substituted C_1-C_6 alkyl and substituted C_3-C_6 cycloalkyl is substituted with one or two of the following:
a) C_{1-4} alkoxy,
b) NR^6R^7,
c) C_{3-6} cycloalkyl,
d) $-NR^6C(O)R^7$,
e) HO,
f) $-S(O)_mR^{6a}$,
g) halogen, or
h) perfluoroalkyl;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4; and
r is 0 to 5, provided that r is 0 when V is hydrogen;

provided that the substituent $(R^8)_r$- V - $A^1(CR^{1a}{}_2)_nA^2(CR^{1a}{}_2)_n$ - is not H;

b) the inhibitors of farnesyl-protein transferase are illustrated by the formula II:



II

wherein:

R^{1a} is selected from: hydrogen or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,

b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$ or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by unsubstituted or substituted aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or -$N(R^{10})_2$;

R^{1c} is selected from:

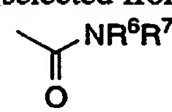
a) hydrogen,

b) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(O)$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-, and

c) unsubstituted or substituted aryl;

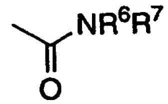
R^3 and R^4 independently selected from H and CH_3;

R^2 is selected from H; OR^{10};


;

or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,
2) heterocycle,
3) OR^6,
4) SR^{6a}, SO_2R^{6a}, or

5)  ;

and R^2, R^3 and R^4 are optionally attached to the same carbon atom;

R^6 and R^7 are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) halogen, or

c) aryl or heterocycle;

R^{6a} is selected from:

C_{1-4} alkyl or C_{3-6} cycloalkyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) halogen, or

c) aryl or heterocycle;

R^8 is independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

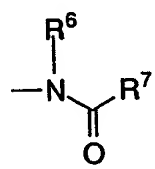
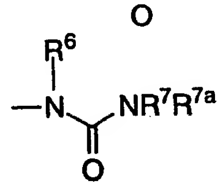
R^{9a} is hydrogen or methyl;

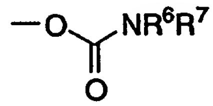
R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

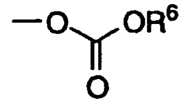
R^{11} is independently selected from C_1-C_6 alkyl and aryl;

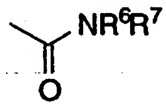
R^{12} is selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted aryl or unsubstituted or substituted heterocycle,

wherein the substituted alkyl, substituted aryl or substituted heterocycle is substituted with one or more of:

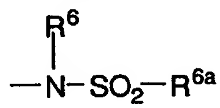
1) aryl or heterocycle, unsubstituted or substituted with:
   a) C_{1-4} alkyl,
   b) $(CH_2)_pOR^6$,
   c) $(CH_2)_pNR^6R^7$,
   d) halogen,
   e) CN,
   f) aryl or heteroaryl,
   g) perfluoro-C_{1-4} alkyl,
   h) SR^{6a}, $S(O)R^{6a}$, SO_2R^{6a},
2) C_{3-6} cycloalkyl,
3) OR^6,
4) SR^{6a}, $S(O)R^{6a}$, or SO_2R^{6a},
5) $-NR^6R^7$,
6)  ,
7)  ,

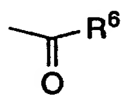
8)  ,

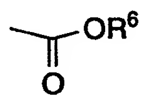
9)  ,

10)  ,

11) $-SO_2-NR^6R^7$,

12)  ,

13)  ,

14)  ,

15) N_3,
16) F,
17) perfluoro-C_{1-4}-alkyl, or
18) C_{1-6}-alkyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, O, -N(R^{10})-, or S(O)$_m$;

V is selected from:

a) hydrogen,
b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,
c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

X is $-CH_2-$ or -C(=O)-;

X^1 is a bond, -C(=O)-, $-NR^6C(=O)-$, $-NR^6-$, -O- or $-S(=O)_m-$;

Y is selected from:

a) hydrogen,

b) $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, $(R^{10})_2N-C(O)-$, CN, NO_2, $(R^{10})_2N-C(NR^{10})-$, $R^{12}C(O)-$, $R^{10}OC(O)-$, N_3, F, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,

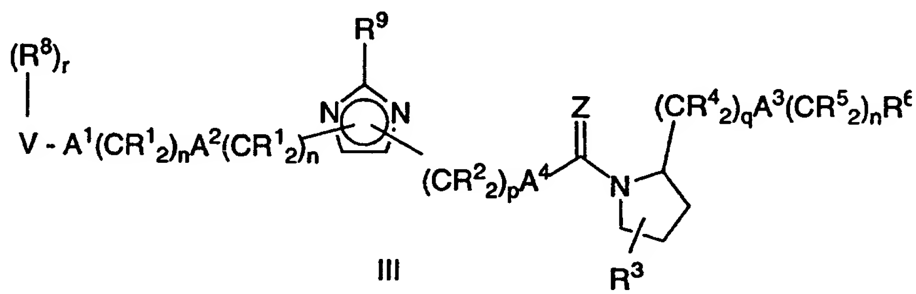
c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, $R^{10}O-$, $R^{10}C(O)NR^{10}-$, $(R^{10})_2N-C(O)-$, $R^{10}C(O)-$ and $R^{10}OC(O)-$;

Z is an unsubstituted or substituted aryl, wherein the substituted aryl is substituted with one or more of the following:

1) C_{1-4} alkyl, unsubstituted or substituted with:
   a) C_{1-4} alkoxy,
   b) NR^6R^7,
   c) C_{3-6} cycloalkyl,
   d) aryl, substituted aryl or heterocycle,
   e) HO,
   f) $-S(O)_mR^{6a}$, or
   g) $-C(O)NR^6R^7$,
2) aryl or heterocycle,
3) halogen,
4) OR^6,

5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) $-S(O)_mR^{6a}$,
10) $-C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4; and
r is 0 to 5, provided that r is 0 when V is hydrogen; and
v is 0, 1 or 2;
(c) a compound represented by formula III:



III

wherein:
R^1 is independently selected from: hydrogen or C_1-C_6 alkyl;
R^2 is independently selected from:
a) hydrogen,
b) substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$- or C_2-C_6 alkenyl,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$-, or $-N(R^{10})_2$;

R^3 is selected from:

a) hydrogen,
b) C_1-C_6 alkyl unsubstituted or substituted by C_2-C_6 alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, N_3, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, fluoro, chloro, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic and C_3-C_{10} cycloalkyl;

R^4 and R^5 are independently selected from:
a) hydrogen,
b) C_1-C_6 alkyl unsubstituted or substituted by C_2-C_6 alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, N_3, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, fluoro, chloro, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic and C_3-C_{10} cycloalkyl;

R^6 is independently selected from:

a) hydrogen,

b) substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, allyloxy, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, $(R^{12})_2NC(O)$- or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^7 is independently selected from

a) hydrogen,

b) unsubstituted or substituted aryl,

c) unsubstituted or substituted heterocycle,

d) unsubstituted or substituted cycloalkyl, and

e) C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and cycloalkyl;

wherein heterocycle is selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, indolyl, quinolinyl, isoquinolinyl, and thienyl;

R^8 is selected from:

a) hydrogen,

b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^9 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkyl substituted with CO_2R^{10}, C_1-C_6 alkyl substituted with aryl, C_1-C_6 alkyl substituted with substituted aryl, C_1-C_6 alkyl substituted with heterocycle, C_1-C_6 alkyl substituted with substituted heterocycle, aryl and substituted aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, $-C(O)NR^7$-, $-NR^7C(O)$-, $-S(O)_2NR^7$-, $-NR^7S(O)_2$-, O, $-N(R^7)$-, or $S(O)_m$;

A^3 is selected from: a bond, $-C(O)NR^7$-, $-NR^7C(O)$-, $-S(O)_2NR^7$-, $-NR^7S(O)_2$- or $-N(R^7)$-;

A^4 is selected from: a bond, O, $-N(R^7)$- or S;

V is selected from:

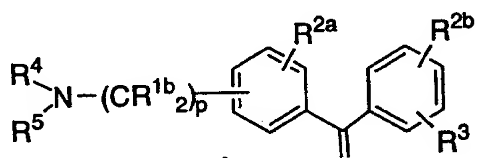
a) hydrogen,
b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,
c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

Z is independently $(R^1)_2$ or O;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
q is 0 or 1; and
r is 0 to 5, provided that r is 0 when V is hydrogen;

d) a compound represented by formula A:



A

wherein:

R^{1a} is selected from: hydrogen or C_1-C_6 alkyl;

R^{1b} is independently selected from:
a) hydrogen,
b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, $-N(R^{10})_2$ or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or -$N(R^{10})_2$;

R2a, R2b and R^3 are independently selected from:

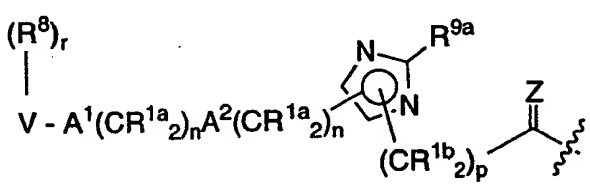
a) hydrogen,

b) C_1-C_6 alkyl unsubstituted or substituted by C_2-C_6 alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, N_3, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted cycloalkyl, alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, halogen or $R^{11}OC(O)NR^{10}$-, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C_3-C_{10} cycloalkyl;

R^4 is



;

R^5 is hydrogen;

R^8 is selected from:

a) hydrogen,

b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} is independently selected from C_1-C_6 alkyl and aryl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl, benzyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^8-, -NR^8C(O)-, O, -$N(R^8)$-, -$S(O)_2N(R^8)$-, -$N(R^8)S(O)_2$-, or $S(O)_m$;

V is selected from:

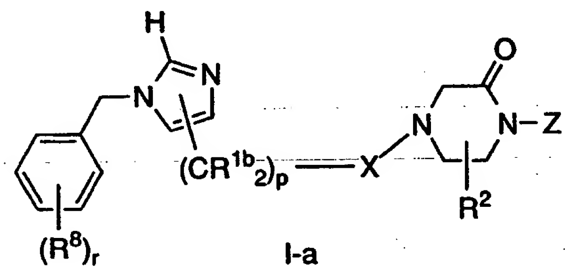
a) hydrogen,
b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,
c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

Z is H_2 or O;
m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is independently 0, 1, 2, 3 or 4; and
r is 0 to 5, provided that r is 0 when V is hydrogen;

or the pharmaceutically acceptable salts thereof.

In a further embodiment of the formula I compounds of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula I-a:



I-a

wherein:

R^{1b} is independently selected from:

a) hydrogen,
b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, $-N(R^{10})_2$ or C_2-C_6 alkenyl,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or $-N(R^{10})_2$;

R^2 is selected from H; unsubstituted or substituted aryl or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,
2) heteroaryl,
3) OR^6, or
4) SR^{6a};

R^6 and R^7 are independently selected from: C_{1-4} alkyl, aryl, and heteroaryl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) halogen,
c) perfluoro-C_{1-4} alkyl, or
d) aryl or heteroaryl;

R^{6a} is selected from:

C_{1-4} alkyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy, or

b) aryl or heteroaryl;

R^8 is independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

X is -CH_2- or -C(=O)-;

Z is an unsubstituted or substituted group selected from aryl, arylmethyl and arylsulfonyl, wherein the substituted group is substituted with one or more of the following:

a) C_{1-4} alkyl, unsubstituted or substituted with: C_{1-4} alkoxy, NR^6R^7, C_{3-6} cycloalkyl, unsubstituted or substituted aryl, heterocycle, HO, -$S(O)_mR^{6a}$, or -$C(O)NR^6R^7$,

b) aryl or heterocycle,

c) halogen,

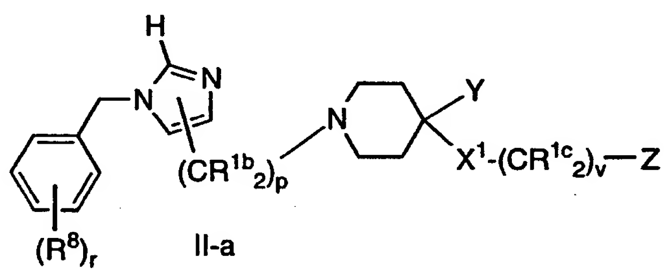
d) OR^6,

e) NR^6R^7,
f) CN,
g) NO_2,
h) CF_3;
i) $-S(O)_mR^{6a}$,
j) $-C(O)NR^6R^7$, or
k) C_3-C_6 cycloalkyl;

m is 0, 1 or 2; and
p is 0, 1, 2, 3 or 4; and
r is 0 to 3;

or the pharmaceutically acceptable salts thereof;

In another embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula II-a:



II-a

wherein:

R^{1b} is independently selected from:
a) hydrogen,
b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, $-N(R^{10})_2$ or C_2-C_6 alkenyl,
c) C_1-C_6 alkyl unsubstituted or substituted by unsubstituted or substituted aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or $-N(R^{10})_2$;

R^{1c} is selected from:
a) hydrogen,

b) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(O)$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-, and

c) unsubstituted or substituted aryl;

R^6, R^7 and R^{7a} are independently selected from:

H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) halogen, or

c) aryl or heterocycle;

R^{6a} is selected from:

C_{1-4} alkyl or C_{3-6} cycloalkyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) halogen, or

c) aryl or heterocycle;

R^8 is independently selected from:

a) hydrogen,

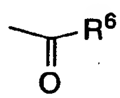
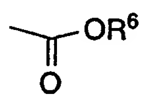
b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and substituted or unsubstituted aryl;

R^{12} is selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted aryl or unsubstituted or substituted heterocycle, wherein the substituted alkyl, substituted aryl or substituted heterocycle is substituted with one or more of:

1) aryl or heterocycle, unsubstituted or substituted with:
   a) C_{1-4} alkyl,
   b) halogen,
   c) CN,
   d) perfluoro-C_{1-4} alkyl,
2) C_{3-6} cycloalkyl,
3) OR^6,
4) SR^{6a}, $S(O)R^{6a}$, or SO_2R^{6a},
5)  ,
6)  ,
7) N_3,
8) F,
9) perfluoro-C_{1-4}-alkyl, or
10) C_{1-6}-alkyl;

X^1 is a bond, -C(=O)- or -S(=O)$_m$-;

Y is selected from:

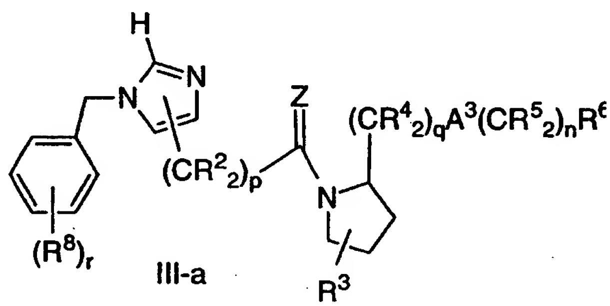
a) hydrogen,
b) $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-C(O)-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{12}C(O)$-, $R^{10}OC(O)$-, N_3, F, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-C(O)-, $R^{10}C(O)$- and $R^{10}OC(O)$-;

Z is an unsubstituted or substituted aryl, wherein the substituted aryl is substituted with one or more of the following:
1) C_{1-4} alkyl, unsubstituted or substituted with:
   a) C_{1-4} alkoxy,
   b) NR^6R^7,
   c) C_{3-6} cycloalkyl,
   d) aryl, substituted aryl or heterocycle,
   e) HO,
   f) -$S(O)_mR^{6a}$, or
   g) -$C(O)NR^6R^7$,
2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) -$S(O)_mR^{6a}$,
10) -$C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl;

m is 0, 1 or 2;
p is 1 or 2 ;
r is 0 to 3; and
v is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

In a further embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula III-a:



III-a

wherein:

R^2 is independently selected from:

a) hydrogen,

b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, $-N(R^{10})_2$ or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or $-N(R^{10})_2$;

R^3 is selected from:

a) hydrogen,

b) C_1-C_6 alkyl unsubstituted or substituted by C_2-C_6 alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, N_3, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, fluoro, chloro, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic and C_3-C_{10} cycloalkyl;

R^4 and R^5 are independently selected from:

a) hydrogen,
b) C_1-C_6 alkyl unsubstituted or substituted by $R^{10}O$- or $-N(R^{10})_2$,
c) substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, fluoro, chloro, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic and C_3-C_{10} cycloalkyl;

R^6 is independently selected from:

a) hydrogen,
b) substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, allyloxy, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $-N(R^{10})_2$, $(R^{12})_2NC(O)$- or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^7 is independently selected from

a) hydrogen,
b) unsubstituted or substituted aryl,
c) unsubstituted or substituted heterocycle,
d) unsubstituted or substituted cycloalkyl, and
e) C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and cycloalkyl;
wherein heterocycle is selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, indolyl, quinolinyl, isoquinolinyl, and thienyl;

R^8 is independently selected from:
a) hydrogen,
b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkyl substituted with CO_2R^{10}, C_1-C_6 alkyl substituted with aryl, C_1-C_6 alkyl substituted with substituted aryl, C_1-C_6 alkyl substituted with heterocycle, C_1-C_6 alkyl substituted with substituted heterocycle, aryl and substituted aryl;

A^3 is selected from: a bond, -$C(O)NR^7$-, -$NR^7C(O)$-, -$S(O)_2NR^7$-,

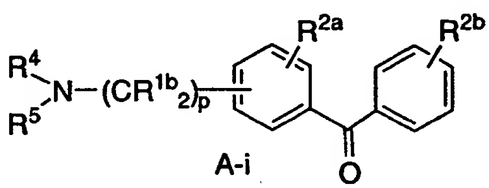
$-NR^7S(O)_2-$ or $-N(R^7)-$;

Z is independently H_2 or O;

m is	0, 1 or 2; and
n is	0, 1, 2, 3 or 4;
p is	0, 1, 2, 3 or 4;
q is	0 or 1; and
r is	0 to 3;

or the pharmaceutically acceptable salts thereof.

In a further embodiment of the formula A compounds of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula A-i:



A-i

wherein:

R^{1b} is independently selected from:

a) hydrogen,

b) aryl, heterocycle, cycloalkyl, $R^{10}O-$, $-N(R^{10})_2$ or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O-$, or $-N(R^{10})_2$;

R^{2a} and R^{2b} are independently selected from:

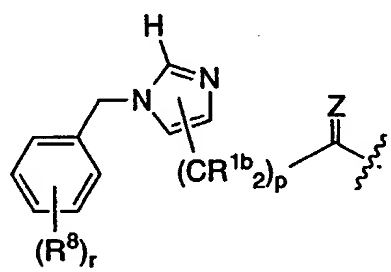
a) hydrogen,

b) C_1-C_6 alkyl unsubstituted or substituted by C_2-C_6 alkenyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, N_3, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,

c) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted cycloalkyl, alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, halogen or $R^{11}OC(O)NR^{10}$-, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclic and C_3-C_{10} cycloalkyl;

R^4 is



;

R^5 is hydrogen;

R^8 is independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 aralkyl and substituted or unsubstituted aryl;

R^{11} is independently selected from C_1-C_6 alkyl, benzyl and aryl;

Z is H_2 or O;
m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is independently 0, 1 or 2; and
r is 0 to 5;

or the pharmaceutically acceptable salts thereof.

Specific compounds which are inhibitors of prenyl-protein transferases and are therefore useful in the present invention include:

1-[2(R)-Amino-3-mercaptopropyl]-2(S)-[(3-pyridyl)methoxyethyl)]-4-(1-naphthoyl)piperazine

1-[2(R)-Amino-3-mercaptopropyl]-2(S)-(benzyloxymethyl)-4-(1-naphthoyl)piperazine

1-[2(R)-Amino-3-mercaptopropyl]-2(S)-(benzyloxymethyl)-4-[7-(2,3-dihydrobenzofuroyl)]piperazine

1-[2(R)-Amino-3-mercaptopropyl]-2(S)-(benzamido)-4-(1-naphthoyl)piperazine

1-[2(R)-Amino-3-mercaptopropyl]-2(S)-[4-(5-dimethylamino-1-naphyhalenesulfonamido)-1-butyl]-4-(1-naphthoyl)piperazine

N-[2(S)-(1-(4-Nitrophenylmethyl)-1H-imidazol-5-ylacetyl)amino-3(S)-methylpentyl]-N-1-naphthylmethyl-glycyl-methionine

N-[2(S)-(1-(4-Nitrophenylmethyl)-1H-imidazol-5-ylacetyl)amino-3(S)-methylpentyl]-N-1-naphthylmethyl-glycyl-methionine methyl ester

N-[2(S)-([1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetylamino)-3(S)-methylpentyl]-N-(1-naphthylmethyl)glycyl-methionine

N-[2(S)-([1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetylamino)-3(S)-methylpentyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(2-naphthylmethyl)imidazol-5-ylmethyl]-piperazine

2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine

1-{[1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetyl}-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine

1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)imidazolylmethyl]-2-piperazinone

1-phenyl-4-[1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl]-piperazin-2-one

1-(3-trifluoromethylphenyl)-4-[1-(4-cyanobenzyl)-1H-imidazol-5-ylmethyl]-piperazin-2-one

1-(3-bromophenyl)-4-[1-(4-cyanobenzyl)-1H-imidazol-5-ylmethyl]-piperazin-2-one

5(S)-(2-[2,2,2-trifluoroethoxy]ethyl)-1-(3-trifluoromethylphenyl)- 4-[1-(4-cyanobenzyl)-4-imidazolylmethyl]-piperazin-2-one

1-(5,6,7,8-tetrahydronaphthyl)-4-[1-(4-cyanobenzyl)-1H-imidazol-5-ylmethyl]-piperazin-2-one

1-(2-methyl-3-chlorophenyl)-4-[1-(4-cyanobenzyl)-4-imidazolylmethyl)]-piperazin-2-one

2(RS)-{[1-(Naphth-2-ylmethyl)-1H-imidazol-5-yl)] acetyl}amino-3-(t-butoxycarbonyl)amino- N-(2-methylbenzyl) propionamide

N-{1-(4-Cyanobenzyl)-1H-imidazol-5-ylmethyl}-4(R)-benzyloxy-2(S)-{N'-acetyl-N'-3-chlorobenzyl}aminomethylpyrrolidine

N-{1-(4-Cyanobenzyl)-1H-imidazol-5-ylethyl}-4(R)-benzyloxy-2(S)-{N'-acetyl-N'-3-chlorobenzyl}aminomethyl pyrrolidine

1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl] pyrrolidin-2(S)-ylmethyl]-(N-2-methylbenzyl)-glycine N'-(3-chlorophenylmethyl) amide

1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl] pyrrolidin-2(S)-ylmethyl]-(N-2-methylbenzyl)-glycine N'-methyl-N'-(3-chlorophenylmethyl) amide

(S)-2-[(1-(4-Cyanobenzyl)-5-imidazolylmethyl)amino]-*N*-(benzyloxycarbonyl)-*N*-(3-chlorobenzyl)-4-(methanesulfonyl)butanamine

1-(3,5-Dichlorobenzenesulfonyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

N-{[1-(4-Cyanobenzyl)-1H-imidazol-5-yl]methyl}-4-(3-methylphenyl)-4-hydroxy piperidine,

N-{[1-(4-Cyanobenzyl)-1H-imidazol-5-yl]methyl}-4-(3-chlorophenyl)-4 hydroxy piperidine,

4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-(2,3-dimethylphenyl)-piperazine-2,3-dione

1-(2-(3-Trifluoromethoxyphenyl)-pyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole

4-{5-[1-(3-Chloro-phenyl)-2-oxo-1,2-dihydro-pyridin-4-ylmethyl]-imidazol-1-ylmethyl}-2-methoxy-benzonitrile

3(R)-3-[1-(4-Cyanobenzyl)imidazol-5-yl-ethylamino]-5-phenyl-1-(2,2,2-trifluoroethyl)-H-benzo[e][1,4] diazepine

3(S)-3-[1-(4-Cyanobenzyl) imidazol-5-yl]-ethylamino]-5-phenyl-1-(2,2,2-trifluoroethyl)-H-benzo[e][1,4] diazepine

N-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine

N-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine methyl ester

N-[1-(1H-Imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine

N-[1-(1H-Imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine methyl ester

2(S)-(4-Acetamido-1-butyl)-1-[2(R)-amino-3-mercaptopropyl]-4-(1-naphthoyl)piperazine

2(RS)-{[1-(Naphth-2-ylmethyl)-1H-imidazol-5-yl)] acetyl}amino-3-(t-butoxycarbonyl)amino- N-cyclohexyl-propionamide

1-{2(R,S)-[1-(4-cyanobenzyl)-1H-imidazol-5-yl]propanoyl}-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine

1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(diphenylmethyl)piperazine

1-(Diphenylmethyl)-3(S)-[N-(1-(4-cyanobenzyl)-2-methyl-1H-imidazol-5-ylethyl)-N-(acetyl)aminomethyl] piperidine

N-[1-(1H-Imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-chlorobenzyl)glycyl-methionine

N-[1-(1H-Imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-chlorobenzyl)glycyl-methionine methyl ester

3(R)-3-[1-(4-Cyanobenzyl)imidazol-5-yl-methylamino]-5-phenyl-1-(2,2,2-trifluoroethyl)-H-benzo[e][1,4] diazepine

1-(3-trifluoromethoxyphenyl)-4-[1-(4-cyanobenzyl)imidazolylmethyl]-2-piperazinone

1-(2,5-dimethylphenyl)-4-[1-(4-cyanobenzyl)imidazolylmethyl]-2-piperazinone

1-(3-methylphenyl)-4-[1-(4-cyanobenzyl)imidazolylmethyl]-2-piperazinone

1-(3-iodophenyl)-4-[1-(4-cyanobenzyl)imidazolylmethyl]-2-piperazinone

1-(3-chlorophenyl)-4-[1-(4-cyano-3-methoxybenzyl)imidazolylmethyl]-2-piperazinone

1-(3-trifluoromethoxyphenyl)-4-[1-(4-cyano-3-methoxybenzyl)imidazolyl methyl]-2-piperazinone

4-[((1-(4-cyanobenzyl)-5-imidazolyl)methyl)amino]benzophenone

1-(1-{[3-(4-cyano-benzyl)-3*H*-imidazol-4-yl]-acetyl}-pyrrolidin-2(S)-ylmethyl)-3(S)-ethyl-pyrrolidine-2(S)-carboxylic acid 3-chloro-benzylamide

or the pharmaceutically acceptable salt thereof.

Compounds within the scope of this invention which have been previously described as inhibitors of farnesyl-protein transferase but which have now been further identified by the instant assays as inhibitors of prenyl-protein transferases and are therefore useful in the

present invention, and methods of synthesis thereof, can be found in the following patents, pending applications and publications, which are herein incorporated by reference:

U.S. Pat. No. 5,736,539 (April 7, 1998);
WO 95/00497 (January 5, 1995)
U.S. Pat. No. 5,652,257 (July 29, 1997);
WO 96/10034 (April 4, 1996); WO 96/30343 (October 3, 1996);
USSN 08/412,829 filed on March 29, 1995;
USSN 08/470,690 filed on June 6, 1995;
USSN 08/600,728 filed on February 28, 1996;
U.S. Pat. No. 5,661,161 (August 26, 1997);
U.S. Pat. No. 5,756,528 (May 6, 1998);
WO 96/39137 (December 12, 1996);
WO 96/37204 (November 28, 1996);
USSN 08/449,038 filed on May 24, 1995;
USSN 08/648,330 filed on May 15, 1996;
WO 97/18813 (May 29, 1997);
USSN 08/749,254 filed on November 15, 1996;
WO 97/38665 (October 23, 1997);
USSN 08/831,308 filed on April 1, 1997;
WO 97/36889 (October 9, 1997);
USSN 08/823,923 filed on March 25, 1997;
WO 97/36901 (October 9, 1997);
USSN 08/827,483 filed on March 27, 1997;
WO 97/36879 (October 9, 1997);
USSN 08/823,920 filed on March 25, 1997;
WO 97/36605 (October 9, 1997);
USSN 08/823,934 filed on March 25, 1997;
WO 98/28980, (July 9, 1998);
USSN 08/997,171 filed on December 22, 1997;
USSN 60/014,791 filed on April 3, 1996; and
USSN 08/831,308, filed on April 4, 1997.

All patents, publications and pending patent applications identified are hereby incorporated by reference.

With respect to the compounds of formulas I-IIIa and A and A-i the following definitions apply:

The term "alkyl" refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 15 carbon atoms unless otherwise defined. It may be straight, branched or cyclic. Preferred straight or branched alkyl groups include methyl, ethyl, propyl, isopropyl, butyl and t-butyl. Preferred cycloalkyl groups include cyclopentyl and cyclohexyl.

When substituted alkyl is present, this refers to a straight, branched or cyclic alkyl group as defined above, substituted with 1-3 groups as defined with respect to each variable.

Heteroalkyl refers to an alkyl group having from 2-15 carbon atoms, and interrupted by from 1-4 heteroatoms selected from O, S and N.

The term "alkenyl" refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 15 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to four non-aromatic (non-resonating) carbon-carbon double bonds may be present. Examples of alkenyl groups include vinyl, allyl, iso-propenyl, pentenyl, hexenyl, heptenyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, isoprenyl, farnesyl, geranyl, geranylgeranyl and the like. Preferred alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted when a substituted alkenyl group is provided.

The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 15 carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds may be present. Preferred alkynyl groups

include ethynyl, propynyl and butynyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted when a substituted alkynyl group is provided.

Aryl refers to aromatic rings e.g., phenyl, substituted phenyl and like groups as well as rings which are fused, e.g., naphthyl and the like. Aryl thus contains at least one ring having at least 6 atoms, with up to two such rings being present, containing up to 10 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms. The preferred aryl groups are phenyl and naphthyl. Aryl groups may likewise be substituted as defined below. Preferred substituted aryls include phenyl and naphthyl substituted with one or two groups. With regard to the farnesyl transferase inhibitors, "aryl" is intended to include any stable monocyclic, bicyclic or tricyclic carbon ring(s) of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of aryl groups include phenyl, naphthyl, anthracenyl, biphenyl, tetrahydronaphthyl, indanyl, phenanthrenyl and the like.

The term "heteroaryl" refers to a monocyclic aromatic hydrocarbon group having 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing at least one heteroatom, O, S or N, in which a carbon or nitrogen atom is the point of attachment, and in which one additional carbon atom is optionally replaced by a heteroatom selected from O or S, and in which from 1 to 3 additional carbon atoms are optionally replaced by nitrogen heteroatoms. The heteroaryl group is optionally substituted with up to three groups.

Heteroaryl thus includes aromatic and partially aromatic groups which contain one or more heteroatoms. Examples of this type are thiophene, purine, imidazopyridine, pyridine, oxazole, thiazole, oxazine, pyrazole, tetrazole, imidazole, pyridine, pyrimidine, pyrazine and triazine. Examples of partially aromatic groups are tetrahydroimidazo[4,5-c]pyridine, phthalidyl and saccharinyl, as defined below.

With regard to the farnesyl transferase inhibitors, the term heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic or stable 11-15 membered tricyclic heterocycle ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothio-pyranyl sulfone, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyridyl N-oxide, pyridonyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinolinyl N-oxide, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, and thienyl. Preferably, heterocycle is selected from imidazolyl, 2-oxopyrrolidinyl, piperidyl, pyridyl and pyrrolidinyl.

With regard to the farnesyl transferase inhibitors, the terms "substituted aryl", "substituted heterocycle" and "substituted cycloalkyl" are intended to include the cyclic group which is substituted with 1 or 2 substituents selected from the group which includes but is not limited to F, Cl, Br, CF_3, NH_2, $N(C_1\text{-}C_6\ alkyl)_2$, NO_2, CN, $(C_1\text{-}C_6\ alkyl)O\text{-}$, -OH, $(C_1\text{-}C_6\ alkyl)S(O)_m\text{-}$, $(C_1\text{-}C_6\ alkyl)C(O)NH\text{-}$, $H_2N\text{-}C(NH)\text{-}$,

(C_1-C_6 alkyl)C(O)-, (C_1-C_6 alkyl)OC(O)-, N_3,(C_1-C_6 alkyl)OC(O)NH- and C_1-C_{20} alkyl.

In the present method, amino acids which are disclosed are identified both by conventional 3 letter and single letter abbreviations as indicated below:

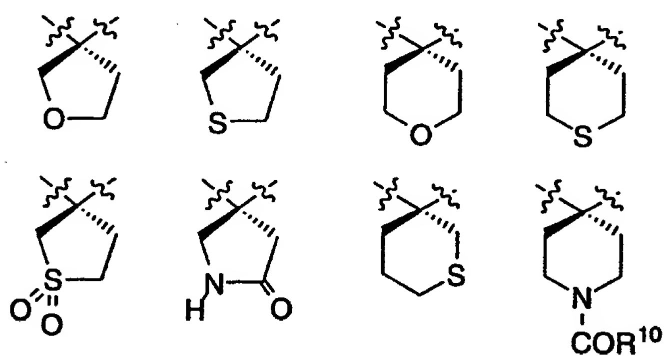
Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartic acid	Asp	D
Asparagine or Aspartic acid	Asx	B
Cysteine	Cys	C
Glutamine	Gln	Q
Glutamic acid	Glu	E
Glutamine or Glutamic acid	Glx	Z
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	Thr	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V

With respect to the term "CAAX" the letter "A" represents an aliphatic amino acid and is not limited to alanine.

The compounds used in the present method may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention. Unless otherwise specified, named amino acids are understood to have the natural "L" stereoconfiguration

When R^2 and R^3 are combined to form - $(CH_2)_u$ -, cyclic moieties are formed. Examples of such cyclic moieties include, but are not limited to:

In addition, such cyclic moieties may optionally include a heteroatom(s). Examples of such heteroatom-containing cyclic moieties include, but are not limited to:



When R^6 and R^7, R^7 and R^{7a}, or are combined to form - $(CH_2)_u$ -, cyclic moieties are formed. Examples of such cyclic moieties include, but are not limited to:

The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like: and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenyl-acetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

It is intended that the definition of any substituent or variable (e.g., R^{10}, Z, n, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. Thus, $-N(R^{10})_2$ represents -NHH, $-NHCH_3$, $-NHC_2H_5$, etc. It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth below.

The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic moiety by conventional chemical methods. Generally, the salts are prepared by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents.

Abbreviations used in the description of the chemistry and in the Examples that follow are:

Ac_2O	Acetic anhydride;
Boc	t-Butoxycarbonyl;
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene;

DMAP	4-Dimethylaminopyridine;
DME	1,2-Dimethoxyethane;
DMF	Dimethylformamide;
EDC	1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide-hydrochloride;
HOBT	1-Hydroxybenzotriazole hydrate;
Et3N	Triethylamine;
EtOAc	Ethyl acetate;
FAB	Fast atom bombardment;
HOOBT	3-Hydroxy-1,2,2-benzotriazin-4(3*H*)-one;
HPLC	High-performance liquid chromatography;
MCPBA	m-Chloroperoxybenzoic acid;
MsCl	Methanesulfonyl chloride;
NaHMDS	Sodium bis(trimethylsilyl)amide;
Py	Pyridine;
TFA	Trifluoroacetic acid;
THF	Tetrahydrofuran.

The compounds are useful in various pharmaceutically acceptable salt forms. The term "pharmaceutically acceptable salt" refers to those salt forms which would be apparent to the pharmaceutical chemist. i.e., those which are substantially non-toxic and which provide the desired pharmacokinetic properties, palatability, absorption, distribution, metabolism or excretion. Other factors, more practical in nature, which are also important in the selection, are cost of the raw materials, ease of crystallization, yield, stability, hygroscopicity and flowability of the resulting bulk drug. Conveniently, pharmaceutical compositions may be prepared from the active ingredients in combination with pharmaceutically acceptable carriers.

Pharmaceutically acceptable salts include conventional non-toxic salts or quarternary ammonium salts formed, e.g., from non-toxic inorganic or organic acids. Non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic,

glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base, in a suitable solvent or solvent combination.

The farnesyl transferase inhibitors of formula I can be synthesized in accordance with Schemes 1-11, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Substituents R, R^a and R^b, as shown in the Schemes, represent the substituents R^2, R^3, R^4, and R^5; however their point of attachment to the ring is illustrative only and is not meant to be limiting.

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Schemes.

Synopsis of Schemes 1-11:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the most part.

Piperazin-5-ones can be prepared as shown in Scheme 1. Thus, the protected suitably substituted amino acid IV can be converted to the corresponding aldehyde V by first forming the amide and then reducing it with LAH. Reductive amination of Boc-protected amino aldehydes V gives rise to compound VI. The intermediate VI can be converted to a piperazinone by acylation with chloroacetyl chloride to

give VII, followed by base-induced cyclization to VIII. Deprotection, followed by reductive alkylation with a protected imidazole carboxaldehyde leads to IX, which can be alkylated with an arylmethylhalide to give the imidazolium salt X. Final removal of protecting groups by either solvolysis with a lower alkyl alcohol, such as methanol, or treatment with triethylsilane in methylene chloride in the presence of trifluoroacetic acid gives the final product XI.

The intermediate VIII can be reductively alkylated with a variety of aldehydes, such as XII. The aldehydes can be prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, **1988**, *67*, 69-75, from the appropriate amino acid (Scheme 2). The reductive alkylation can be accomplished at pH 5-7 with a variety of reducing agents, such as sodium triacetoxyborohydride or sodium cyanoborohydride in a solvent such as dichloroethane, methanol or dimethylformamide. The product XIII can be deprotected to give the final compounds XIV with trifluoroacetic acid in methylene chloride. The final product XIV is isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine XIV can further be selectively protected to obtain XV, which can subsequently be reductively alkylated with a second aldehyde to obtain XVI. Removal of the protecting group, and conversion to cyclized products such as the dihydroimidazole XVII can be accomplished by literature procedures.

Alternatively, the imidazole acetic acid XVIII can be converted to the acetate XIX by standard procedures, and XIX can be first reacted with an alkyl halide, then treated with refluxing methanol to provide the regiospecifically alkylated imidazole acetic acid ester XX (Scheme 3). Hydrolysis and reaction with piperazinone VIII in the presence of condensing reagents such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) leads to acylated products such as XXI.

If the piperazinone VIII is reductively alkylated with an aldehyde which also has a protected hydroxyl group, such as XXII in Scheme 4, the protecting groups can be subsequently removed

to unmask the hydroxyl group (Schemes 4, 5). The alcohol can be oxidized under standard conditions to *e.g.* an aldehyde, which can then be reacted with a variety of organometallic reagents such as Grignard reagents, to obtain secondary alcohols such as XXIV. In addition, the fully deprotected amino alcohol XXV can be reductively alkylated (under conditions described previously) with a variety of aldehydes to obtain secondary amines, such as XXVI (Scheme 5), or tertiary amines.

The Boc protected amino alcohol XXIII can also be utilized to synthesize 2-aziridinylmethylpiperazinones such as XXVII (Scheme 6). Treating XXIII with 1,1'-sulfonyldiimidazole and sodium hydride in a solvent such as dimethylformamide led to the formation of aziridine XXVII. The aziridine reacted in the presence of a nucleophile, such as a thiol, in the presence of base to yield the ring-opened product XXVIII.

In addition, the piperazinone VIII can be reacted with aldehydes derived from amino acids such as O-alkylated tyrosines, according to standard procedures, to obtain compounds such as XXX (Scheme 7). When R' is an aryl group, XXX can first be hydrogenated to unmask the phenol, and the amine group deprotected with acid to produce XXXI. Alternatively, the amine protecting group in XXX can be removed, and O-alkylated phenolic amines such as XXXII produced.

Scheme 8 illustrates the use of an optionally substituted homoserine lactone XXXIII to prepare a Boc-protected piperazinone XXXVII. Intermediate XXXVII may be deprotected and reductively alkylated or acylated as illustrated in the previous Schemes. Alternatively, the hydroxyl moiety of intermediate XXXVII may be mesylated and displaced by a suitable nucleophile, such as the sodium salt of ethane thiol, to provide an intermediate XXXVIII. Intermediate XXXVII may also be oxidized to provide the carboxylic acid on intermediate IXL, which can be utilized form an ester or amide moiety.

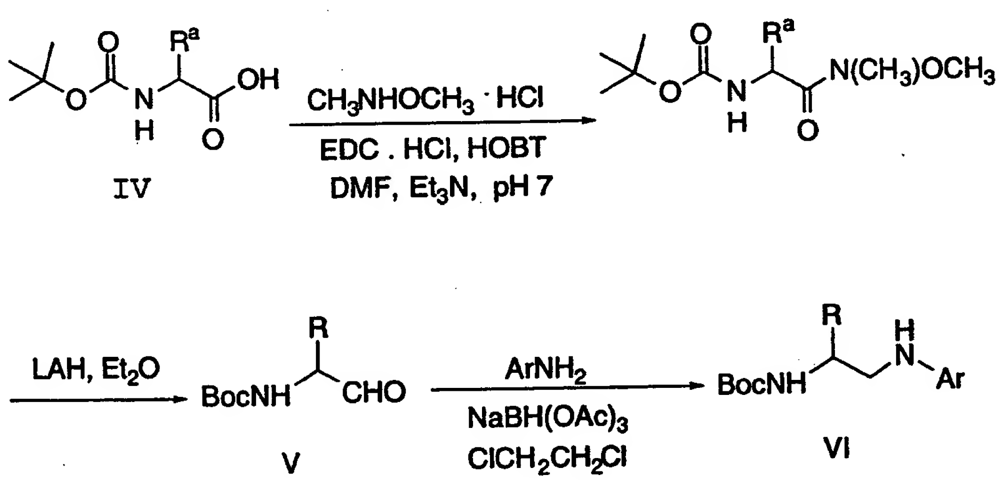
N-Aralkyl-piperazin-5-ones can be prepared as shown in Scheme 9. Reductive amination of Boc-protected amino aldehydes V (prepared from III as described previously) gives rise to compound XL. This is then reacted with bromoacetyl bromide under Schotten-Baumann conditions; ring closure is effected with a base such as sodium hydride

in a polar aprotic solvent such as dimethylformamide to give XLI. The carbamate protecting group is removed under acidic conditions such as trifluoroacetic acid in methylene chloride, or hydrogen chloride gas in methanol or ethyl acetate, and the resulting piperazine can then be carried on to final products as described in Schemes 1-7.

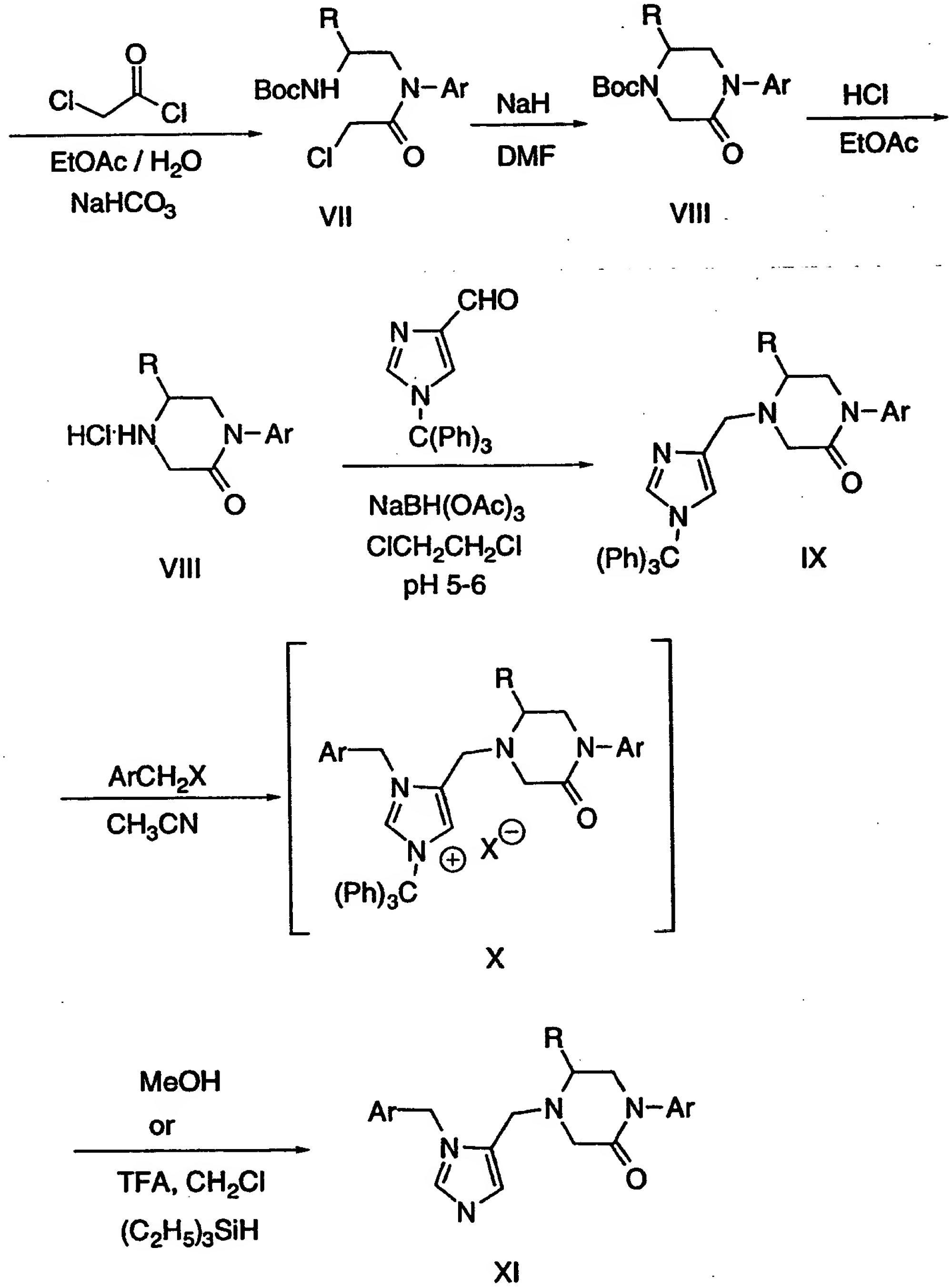
The isomeric piperazin-3-ones can be prepared as described in Scheme 10. The imine formed from arylcarboxamides XLII and 2-aminoglycinal diethyl acetal (XLIII) can be reduced under a variety of conditions, including sodium triacetoxyborohydride in dichloroethane, to give the amine XLIV. Amino acids I can be coupled to amines XLIV under standard conditions, and the resulting amide XLV when treated with aqueous acid in tetrahydrofuran can cyclize to the unsaturated XLVI. Catalytic hydrogenation under standard conditions gives the requisite intermediate XLVII, which is elaborated to final products as described in Schemes 1-7.

Amino acids of the general formula IL which have a side-chain not found in natural amino acids may be prepared by the reactions illustrated in Scheme 11 starting with the readily prepared imine XLVIII.

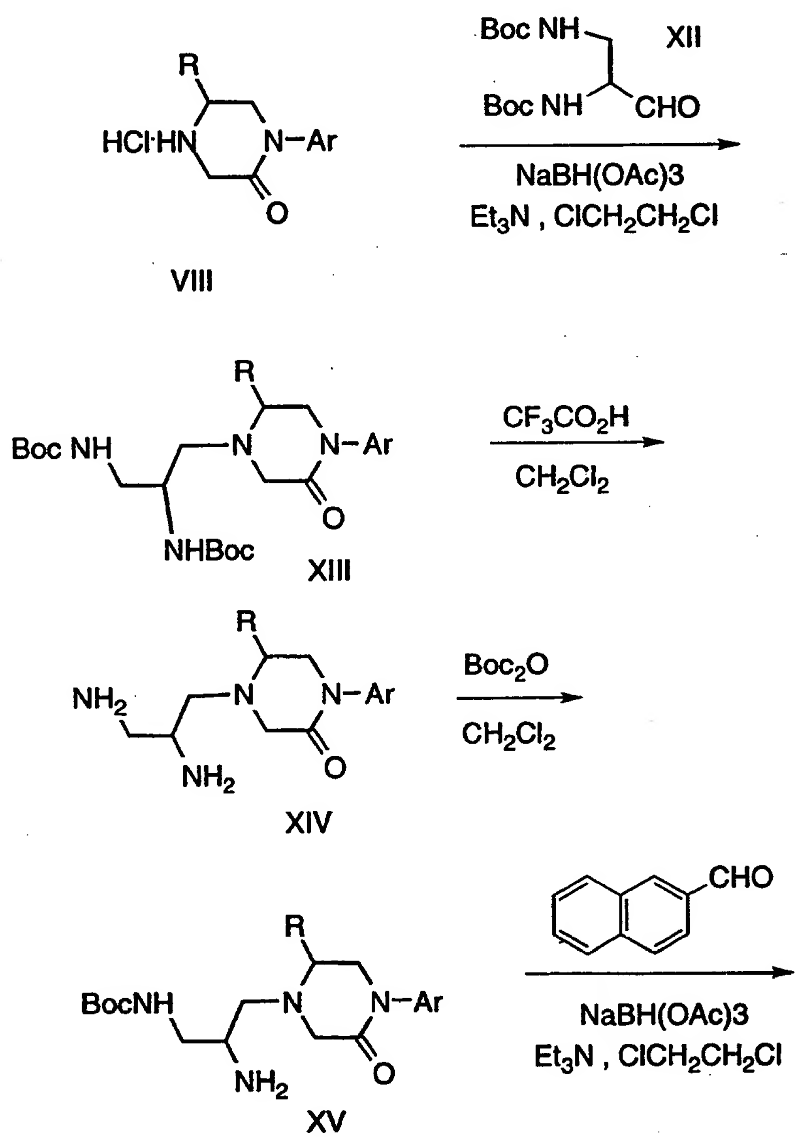
SCHEME 1



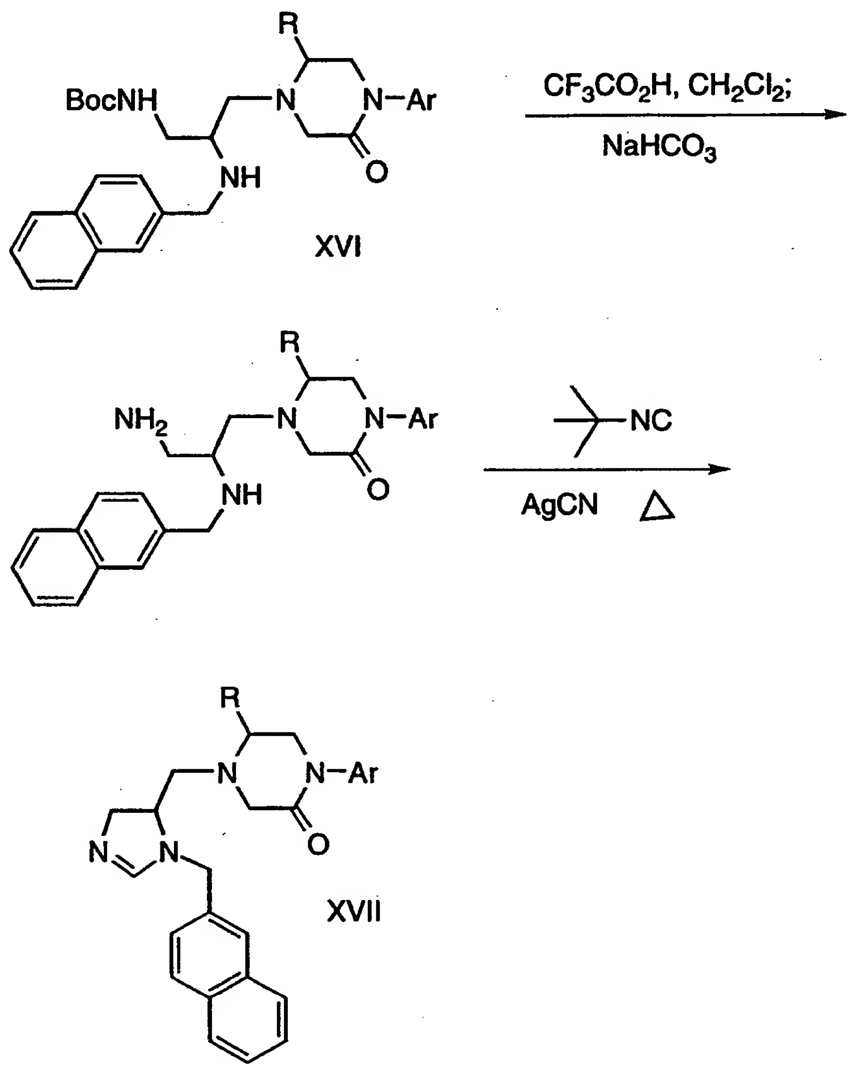
SCHEME 1 (continued)



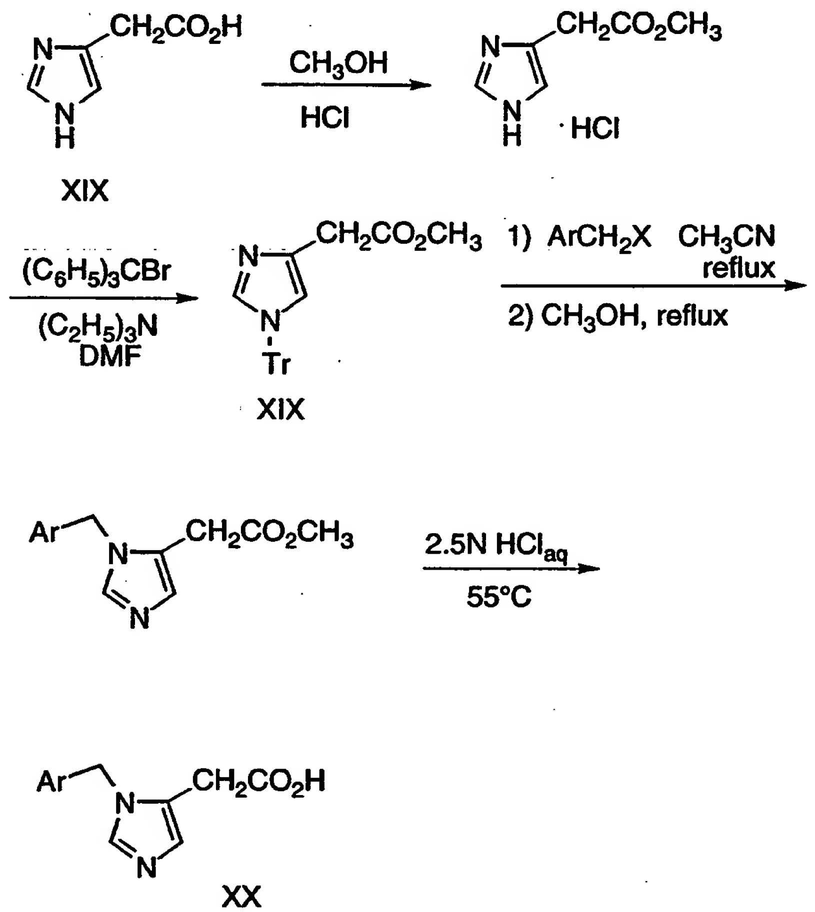
SCHEME 2



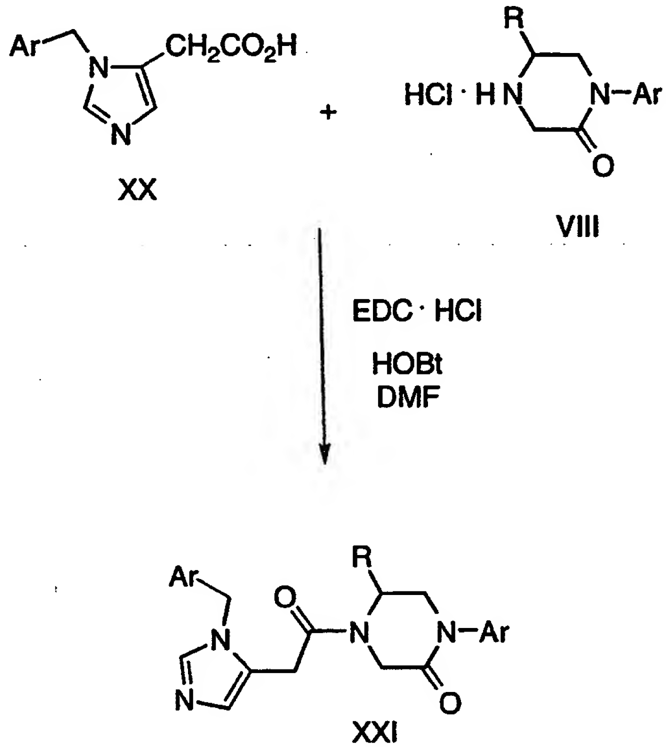
SCHEME 2 (continued)



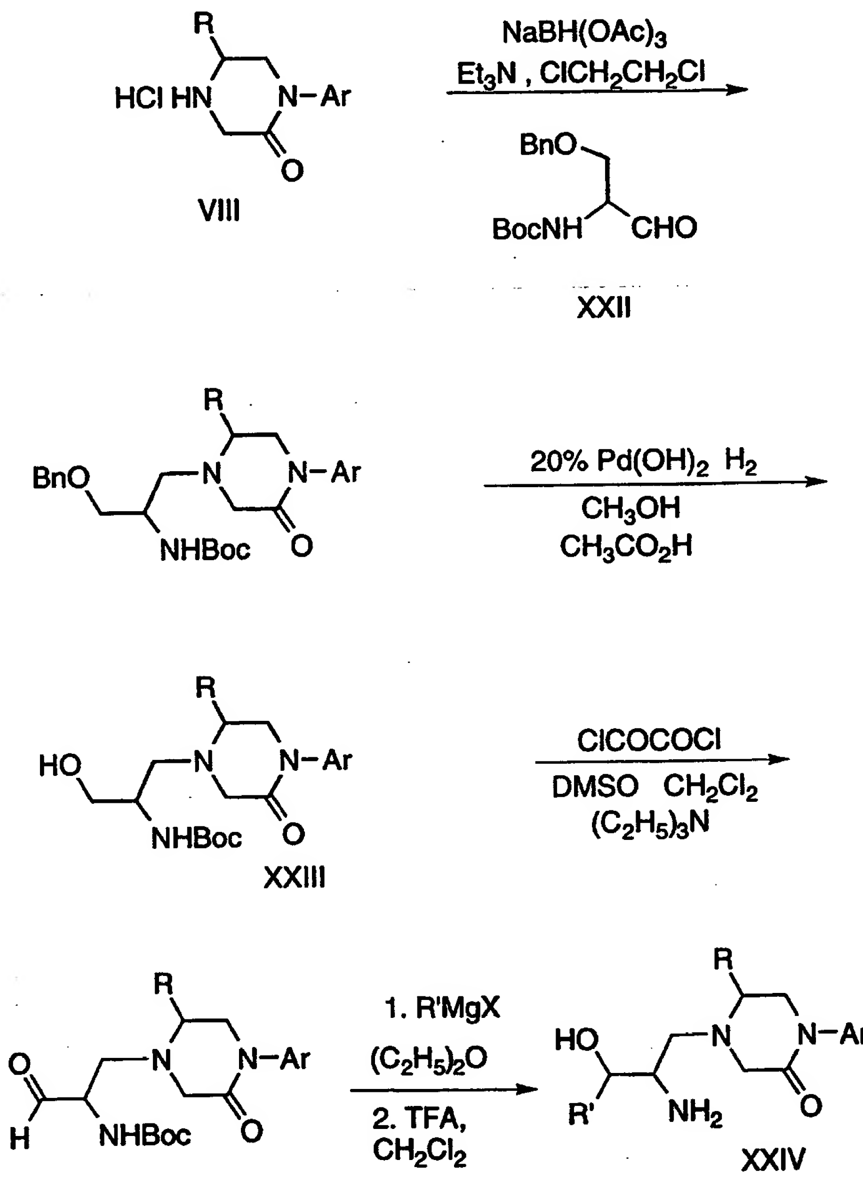
SCHEME 3


CH2CO2H
CH3OH
HCl
CH2CO2CH3
· HCl
XIX
(C6H5)3CBr
(C2H5)3N
DMF
CH2CO2CH3
Tr
XIX
1) ArCH2X CH3CN reflux
2) CH3OH, reflux
Ar
CH2CO2CH3
2.5N HClaq
55°C
Ar
CH2CO2H
XX

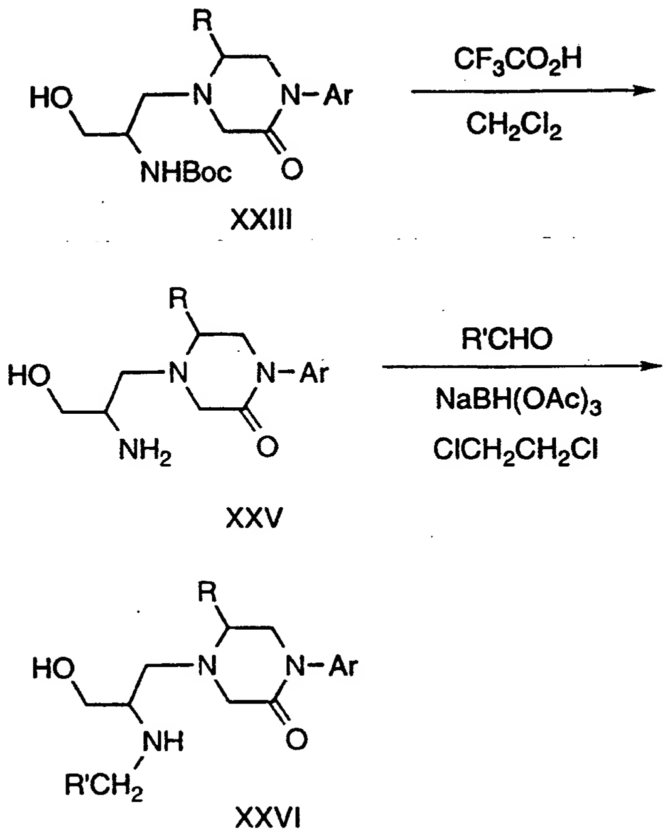
SCHEME 3 (continued)



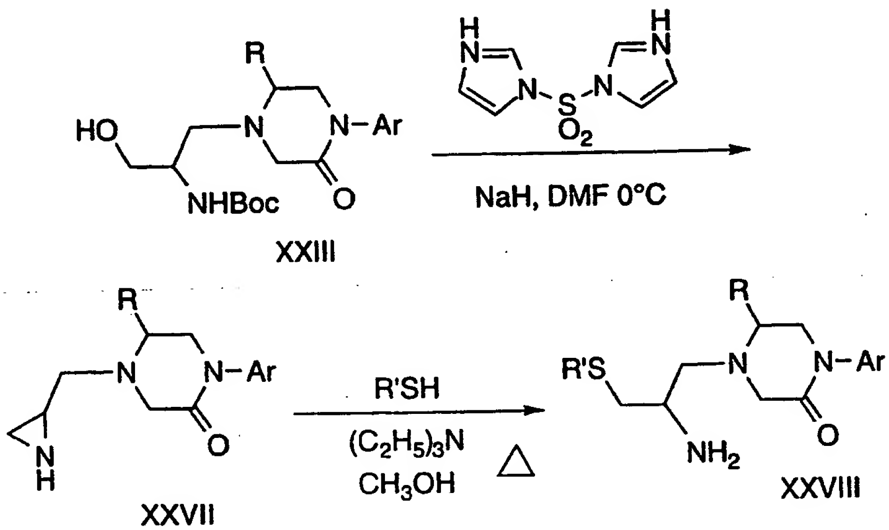
SCHEME 4


R
HCl HN
N−Ar
O
VIII
NaBH(OAc)3
Et3N , ClCH2CH2Cl
BnO
BocNH
CHO
XXII
BnO
N
NHBoc
20% Pd(OH)2 H2
CH3OH
CH3CO2H
HO
XXIII
ClCOCOCl
DMSO CH2Cl2
(C2H5)3N
H
1. R'MgX
(C2H5)2O
2. TFA,
CH2Cl2
R'
NH2
XXIV

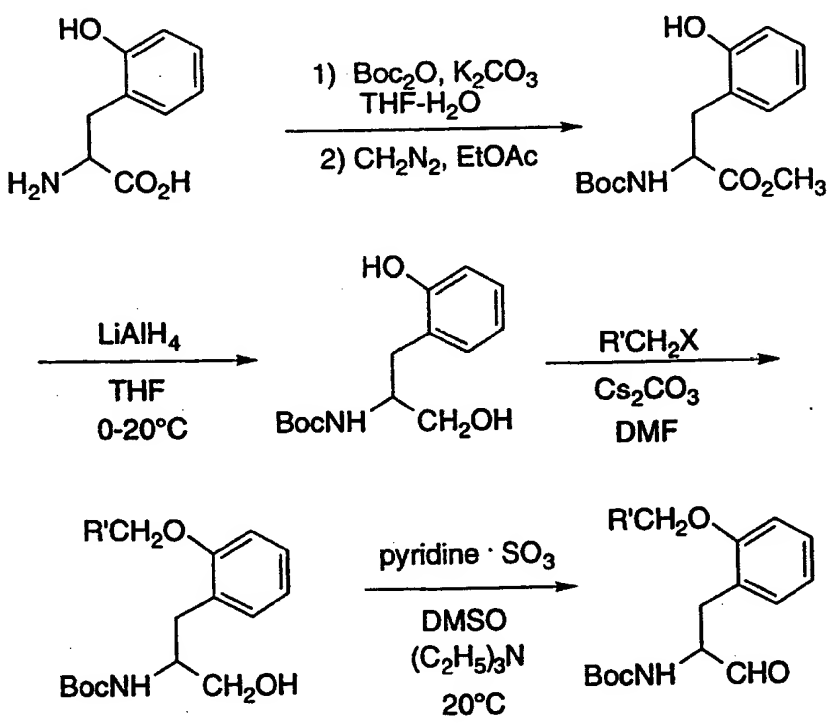
SCHEME 5



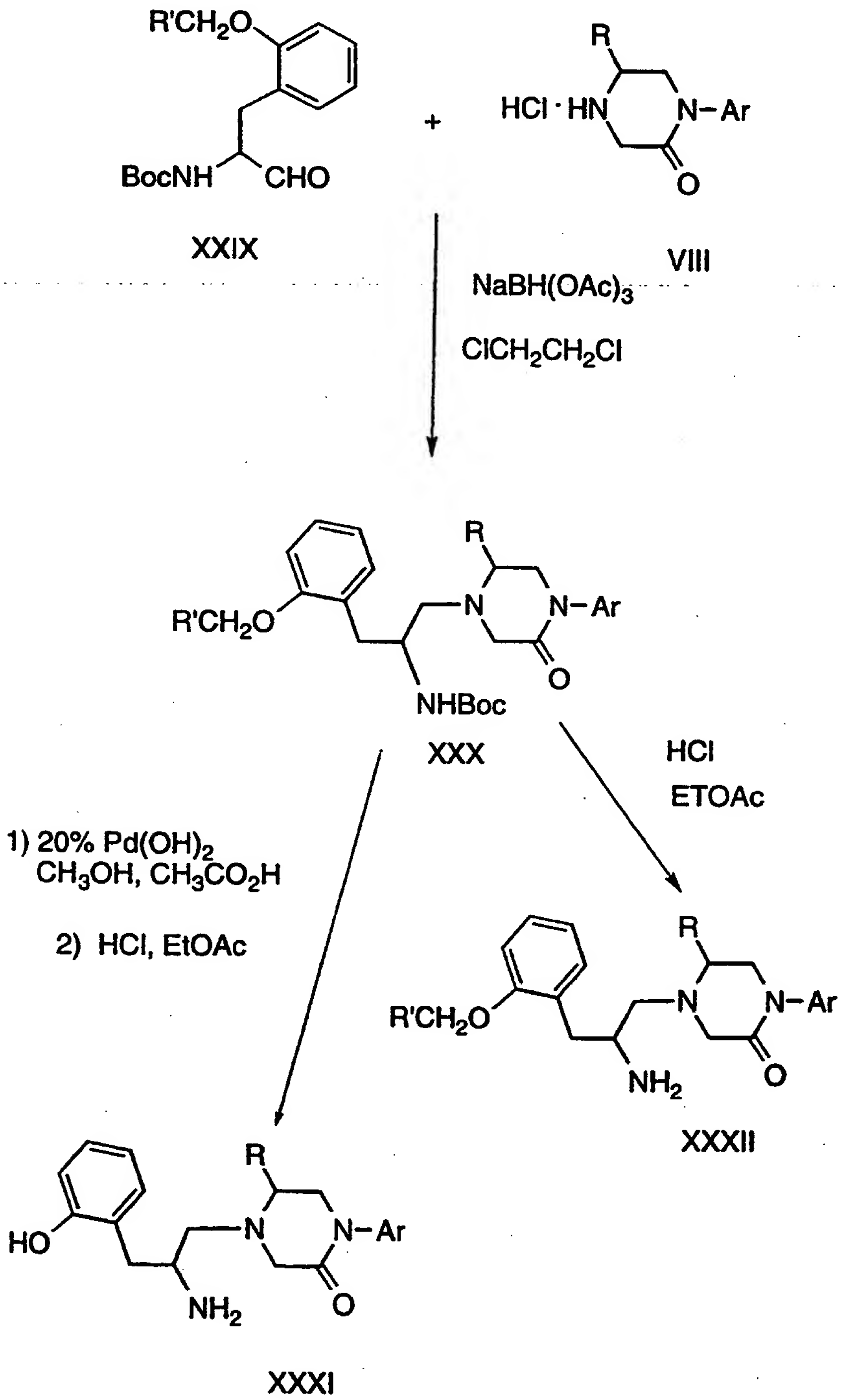
SCHEME 6



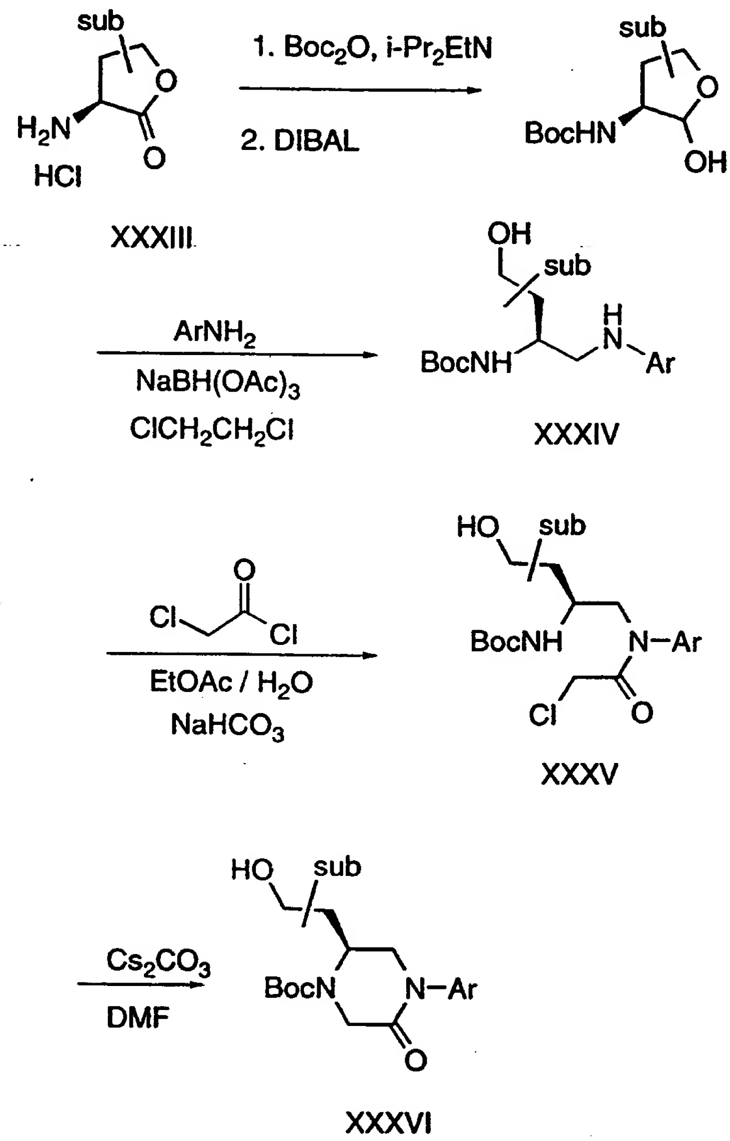
SCHEME 7



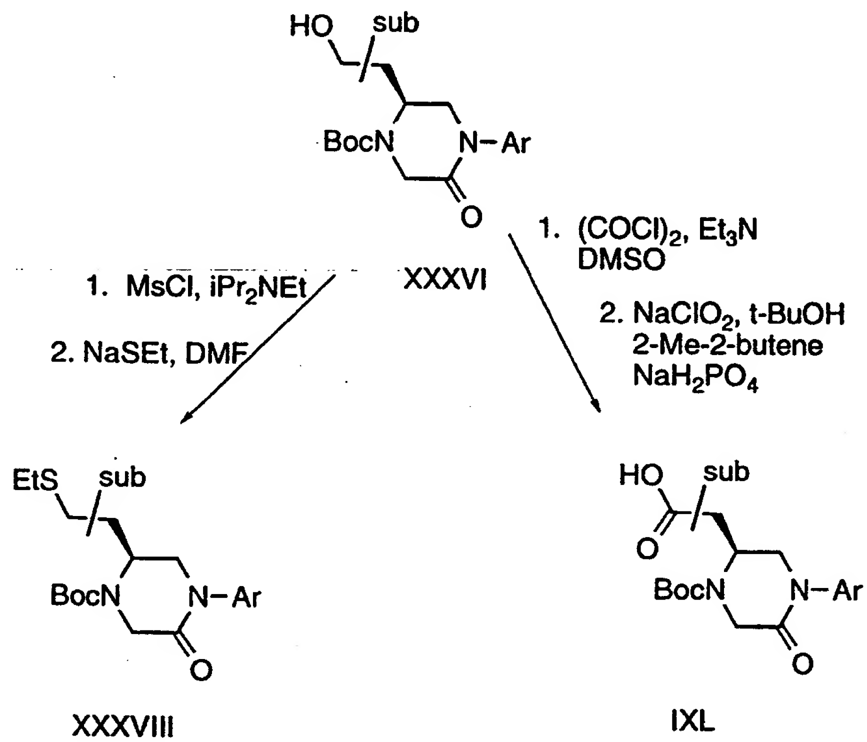
SCHEME 7 (continued)



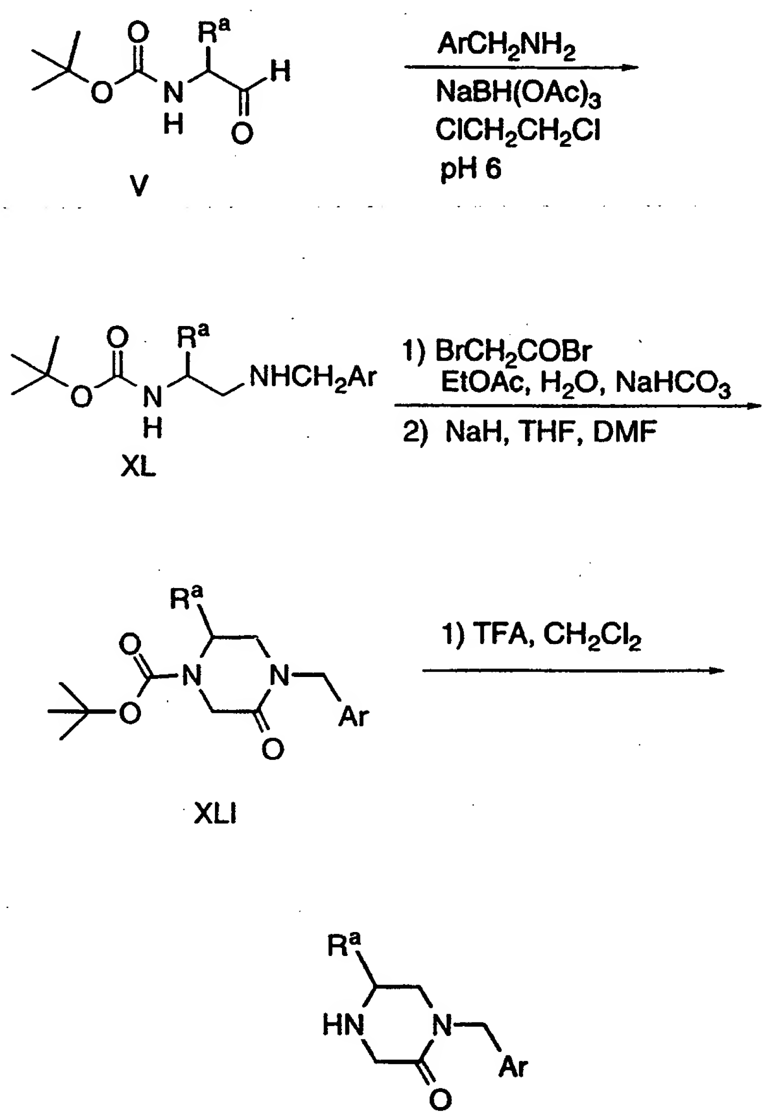
SCHEME 8


sub
H2N
HCl
1. Boc2O, i-Pr2EtN
2. DIBAL
BocHN
OH
XXXIII
ArNH2
NaBH(OAc)3
ClCH2CH2Cl
BocNH
N
Ar
XXXIV
EtOAc / H2O
NaHCO3
HO
N-Ar
Cl
XXXV
Cs2CO3
DMF
BocN
XXXVI

SCHEME 8 (continued)

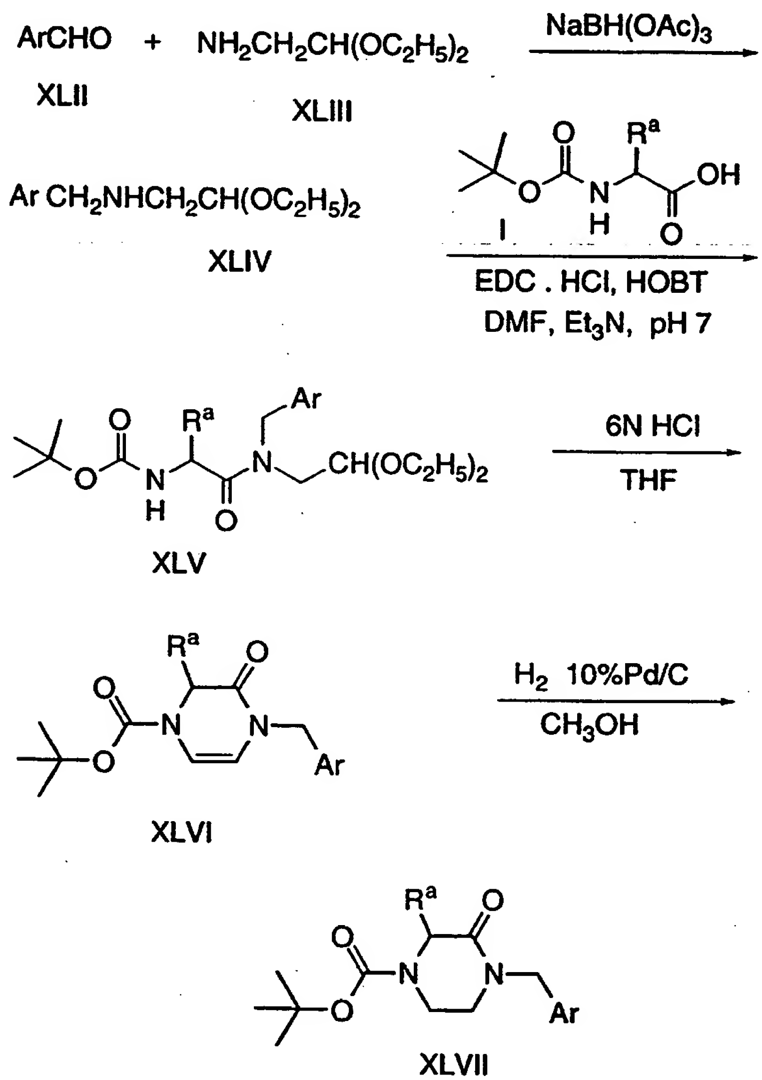


SCHEME 9

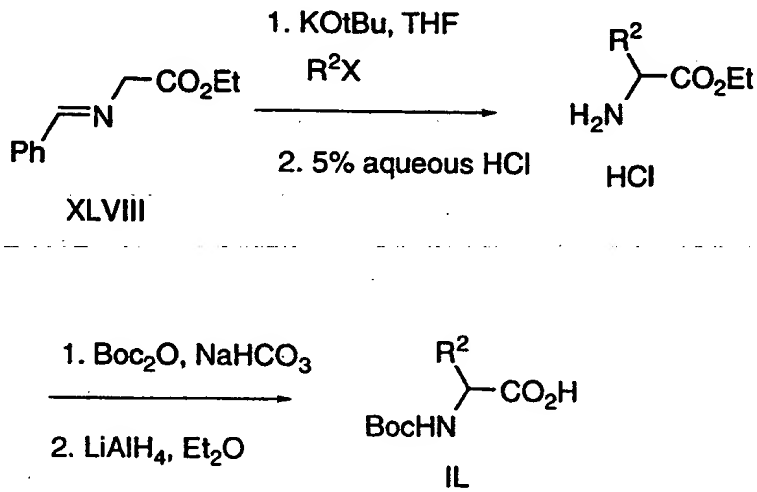


V
ArCH2NH2
NaBH(OAc)3
ClCH2CH2Cl
pH 6
XL
1) BrCH2COBr
EtOAc, H2O, NaHCO3
2) NaH, THF, DMF
XLI
1) TFA, CH2Cl2

SCHEME 10



SCHEME 11



Reactions used to generate the compounds of the formula (II) are prepared by employing reactions as shown in the Schemes 16-37, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Substituents R^a and R^b, as shown in the Schemes, represent the substituents R^2, R^3, R^4, and R^5; substituent "sub" represents a suitable substituent on the substituent Z. The point of attachment of such substituents to a ring is illustrative only and is not meant to be limiting.

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Schemes.

Synopsis of Schemes 16-37:

The requisite intermediates utilized as starting material in the Schemes hereinbelow are in some cases commercially available, or can be prepared according to literature procedures. In Scheme 16, for example, a suitably substituted Boc protected isonipecotate LI may be

deprotonated and then treated with a suitably substituted alkylating group, such as a suitably substituted benzyl bromide, to provide the gem disubstituted intermediate LIII. Deprotection and reduction provides the hydroxymethyl piperidine LIV which can be utilized is synthesis of compounds of the invention or which may be nitrogen-protected and methylated to give the intermediate LV.

As shown in Scheme 17, the protected piperidine intermediate LIII can be deprotected and reductively alkylated with aldehydes such as 1-trityl-4-imidazolyl-carboxaldehyde or 1-trityl-4-imidazolylacetaldehyde, to give products such as LVI. The trityl protecting group can be removed from LVI to give LVII, or alternatively, LVI can first be treated with an alkyl halide then subsequently deprotected to give the alkylated imidazole LVIII.

The deprotected intermediate LIII can also be reductively alkylated with a variety of other aldehydes and acids as shown above in Schemes 4-7.

An alternative synthesis of the hydroxymethyl intermediate LIV and utilization of that intermediate in the synthesis of the instant compounds which incorporate the preferred imidazolyl moiety is illustrated in Scheme 18. Scheme 19 illustrates the reductive alkylation of intermediate LIV to provide a 4-cyanobenzylimidazolyl substituted piperidine. The cyano moiety may be selectively hydrolyzed with sodium borate to provide the corresponding amido compound of the instant invention.

Scheme 20 alternative preparation of the methyl ether intermediate LV and the alkylation of LV with a suitably substituted imidazolylmethyl chloride to provide the instant compound. Preparation of the homologous 1-(imidazolylethyl)piperidine is illustrated in Scheme 21.

Specific substitution on the piperidine of the compounds of the instant invention may be accomplished as illustrated in Scheme 22. Thus, metal-halogen exchange coupling of a butynyl moiety to an isonicotinate, followed by hydrogenation, provides the 2-butylpiperidine

intermediate that can then undergo the reactions previously described to provide the compound of the instant invention.

Incorporation of a 4-amido moiety for LV is illustrated in Scheme 23.

Scheme 24 illustrates the synthesis of the instant compounds wherein the moiety Z is attached directly to the piperidine ring. Thus the piperidone LIX is treated with a suitably substituted phenyl Grignard reagent to provide the gem disubstituted piperidine LX. Deprotection provides the key intermediate LXI. Intermediate LXI may be acetylated as described above to provide the instant compound LXII (Scheme 25).

As illustrated in Scheme 26, the protected piperidine LX may be dehydrated and then hydroborated to provide the 3-hydroxypiperidine LXIII. This compound may be deprotected and further derivatized to provide compounds of the instant invention (as shown in Scheme 27) or the hydroxyl group may be alkylated, as shown in Scheme 26, prior to deprotection and further manipulation.

The dehydration product may also be catalytically reduced to provide the des-hydroxy intermediate LXV, as shown in Scheme 28, which can be processed via the reactions illustrated in the previous Schemes.

Schemes 29 and 30 illustrate further chemical manipulations of the 4-carboxylic acid functionality to provide instant compounds wherein the substituent Y is an acetylamine or sulfonamide moiety.

Scheme 31 illustrates incorporation of a nitrile moiety in the 4-position of the piperidine of the compounds of formula II. Thus, the hydroxyl moiety of a suitably substituted 4-hydroxypiperidine is substituted with nitrile to provide intermediate LXVI, which can undergo reactions previously described in Schemes 17-21.

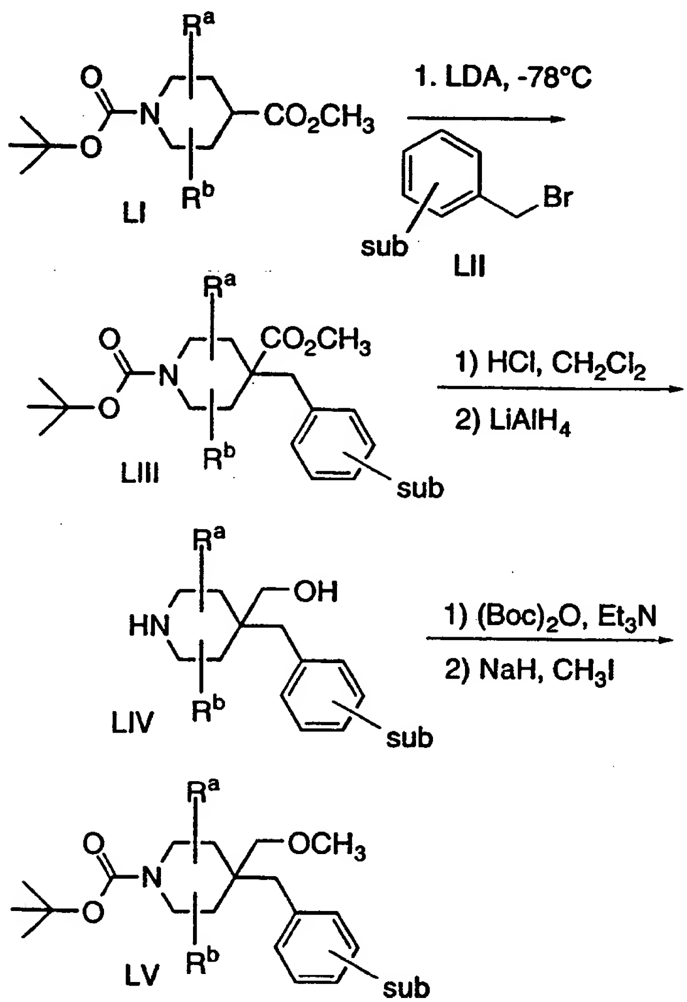
Scheme 32 illustrates the preparation of several pyridyl intermediates that may be utilized with the piperidine intermediates such as compound LI in Scheme 16 to provide the instant compounds. Scheme 33 shows a generalized reaction sequence which utilizes such pyridyl intermediates.

Compounds of the instant invention wherein X^1 is a carbonyl moiety may be prepared as shown in Scheme 34. Intermediate LXVII may undergo subsequent reactions as illustrated in Schemes 17-21 to provide the instant compounds. Preparation of the instant compounds wherein X^1 is sulfur in its various oxidation states is shown in Scheme 35. Intermediates LXVIII-LXXI may undergo the previously described reactions to provide the instant compounds.

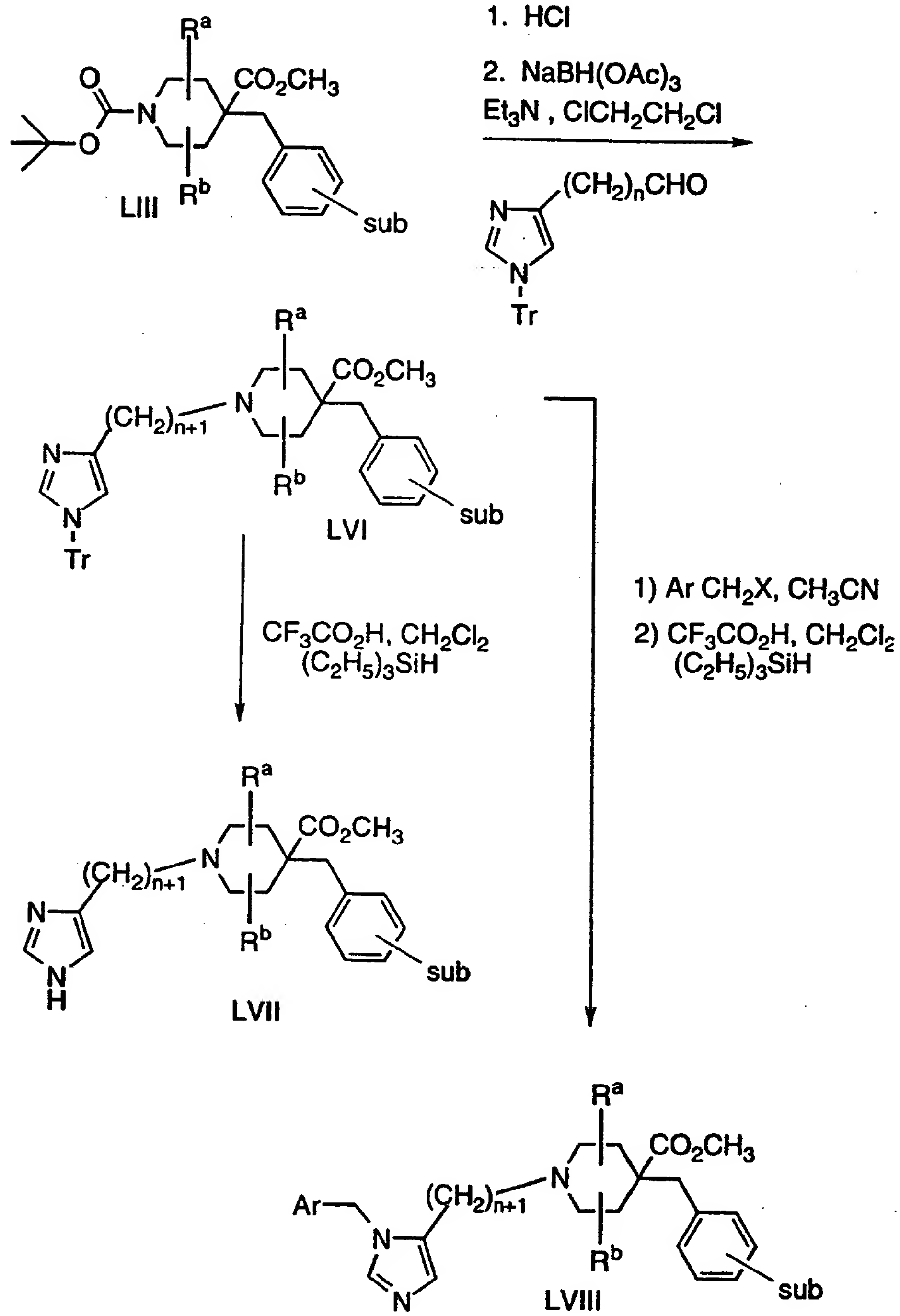
Scheme 36 illustrated preparation of compounds of the formula A wherein Y is hydrogen. Thus, suitably substituted isonipecotic acid may be treated with N,O-dimethylhydroxylamine and the intermediate LXXII reacted with a suitably substituted phenyl Grignard reagent to provide intermediate LXXIII. That intermediate may undergo the reactions previously described in Schemes 17-21 and may be further modified by reduction of the phenyl ketone to provide the alcohol LXXIV.

Compounds of the instant invention wherein X^1 is an amine moiety may be prepared as shown in Scheme 37. Thus the N-protected 4-piperidinone may be reacted with a suitably substituted aniline in the presence of trimethylsilylcyanide to provide the 4-cyano-4-aminopiperidine LXXV. Intermediate LXXV may then be converted in sequence to the corresponding amide LXXVI, ester LXXVII and alcohol LXXVIII. Intermediates LXXVI-LXXVIII can be deprotected and can then undergo the reactions previously described in Schemes 17-21 to provide the compounds of the instant invention.

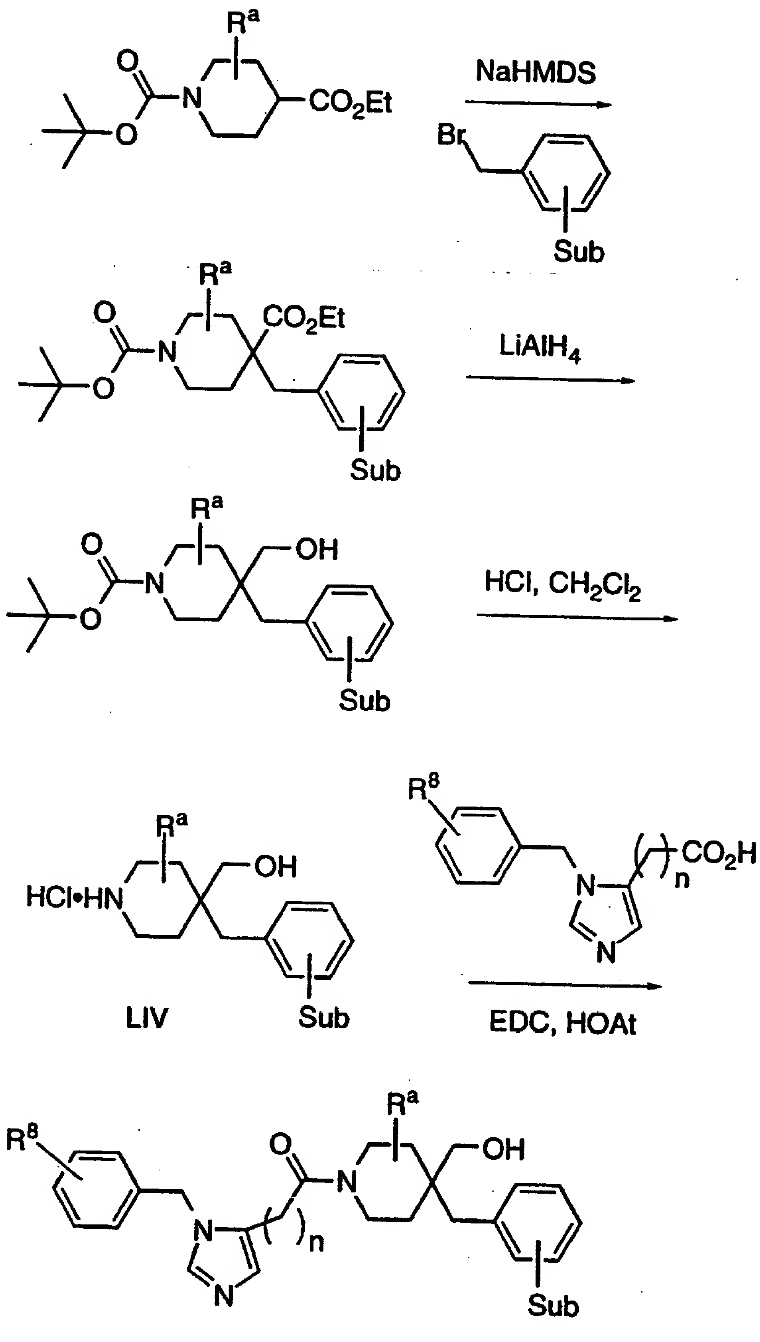
SCHEME 16



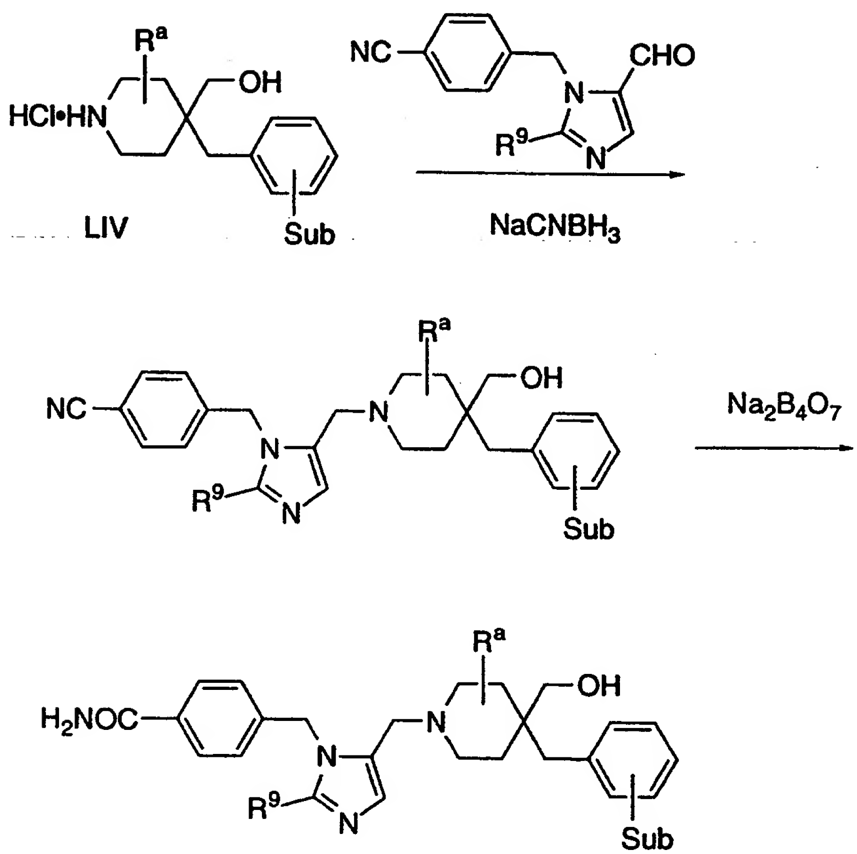
SCHEME 17


1. HCl
2. NaBH(OAc)3
Et3N , ClCH2CH2Cl
(CH2)nCHO
LIII
LVI
CF3CO2H, CH2Cl2
(C2H5)3SiH
1) Ar CH2X, CH3CN
2) CF3CO2H, CH2Cl2
(C2H5)3SiH
LVII
LVIII

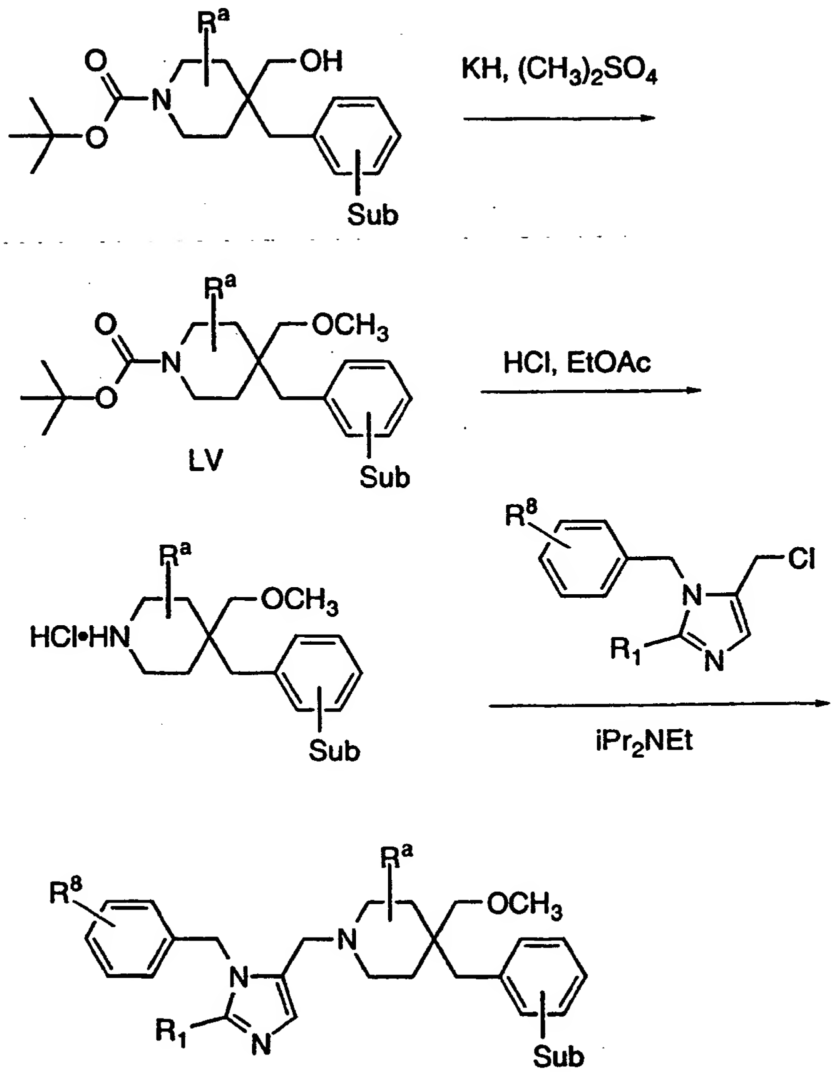
SCHEME 18



SCHEME 19

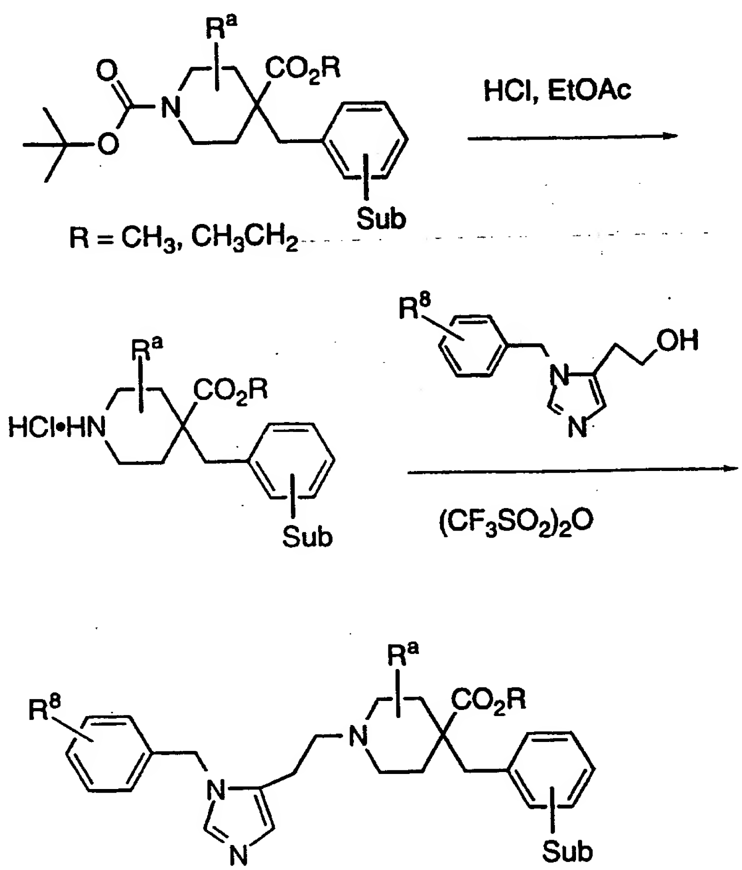


SCHEME 20



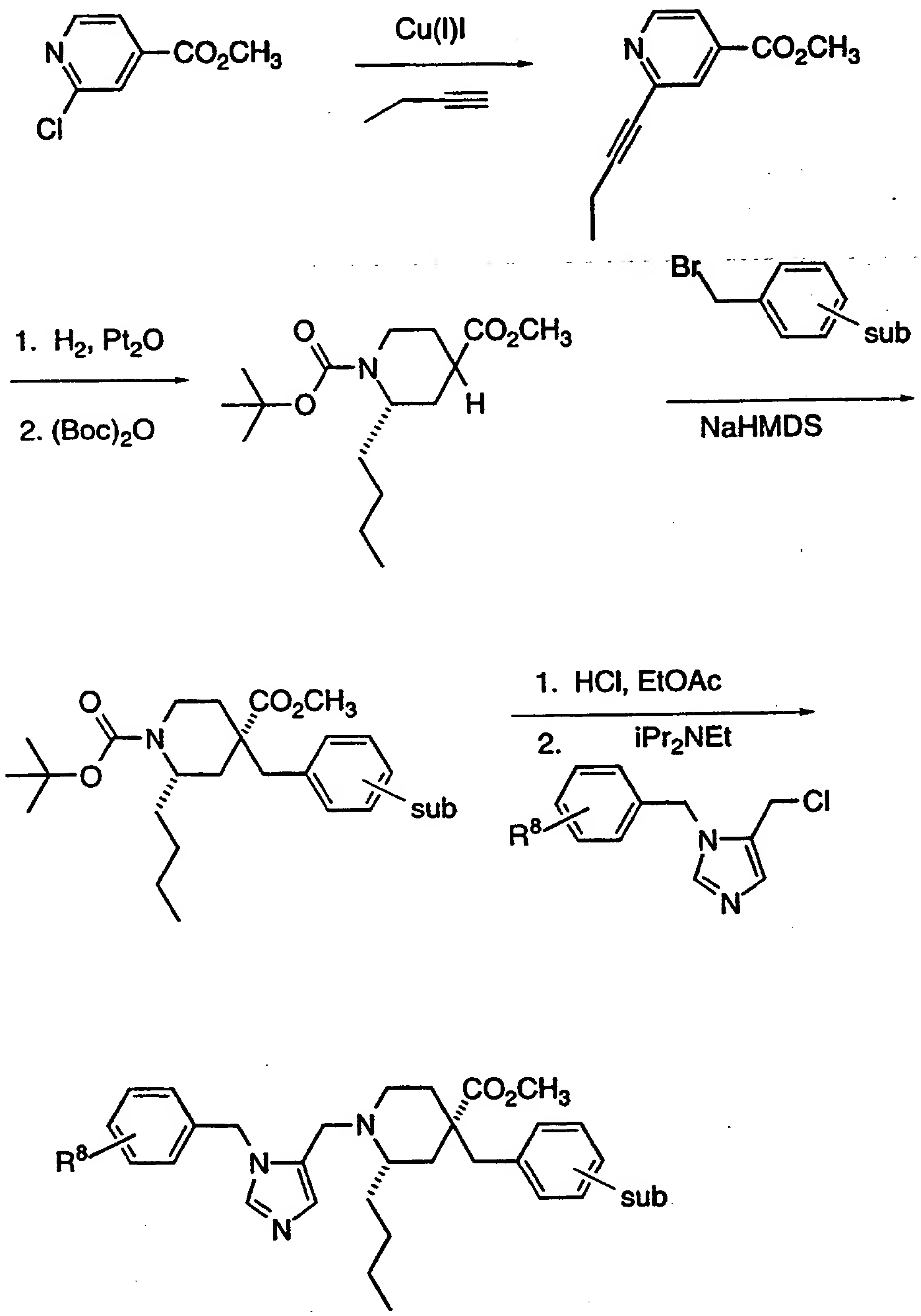
R^a
OH
O
N
O
Sub
KH, (CH3)2SO4
OCH3
HCl, EtOAc
LV
HCl•HN
R8
N
Cl
R1
iPr2NEt

SCHEME 21



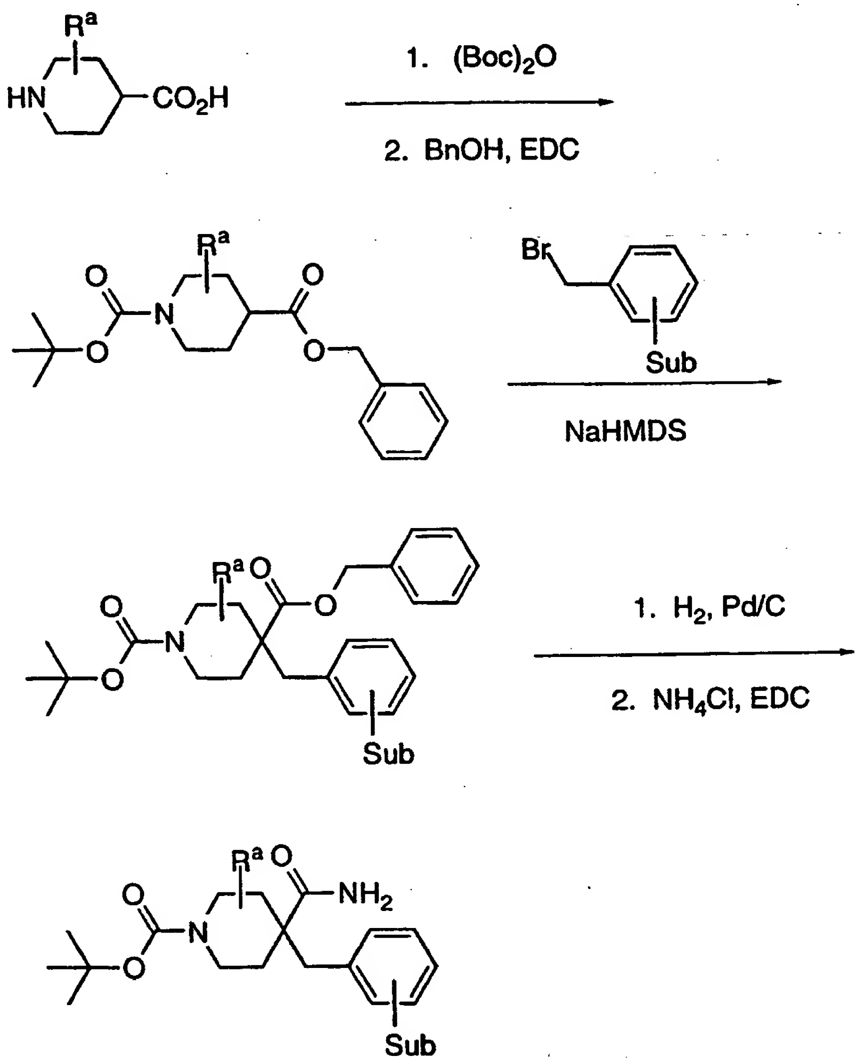
R^a
CO2R
O
N
O
Sub
HCl, EtOAc
R = CH3, CH3CH2
R8
OH
N
N
HCl•HN
(CF3SO2)2O
R8

SCHEME 22

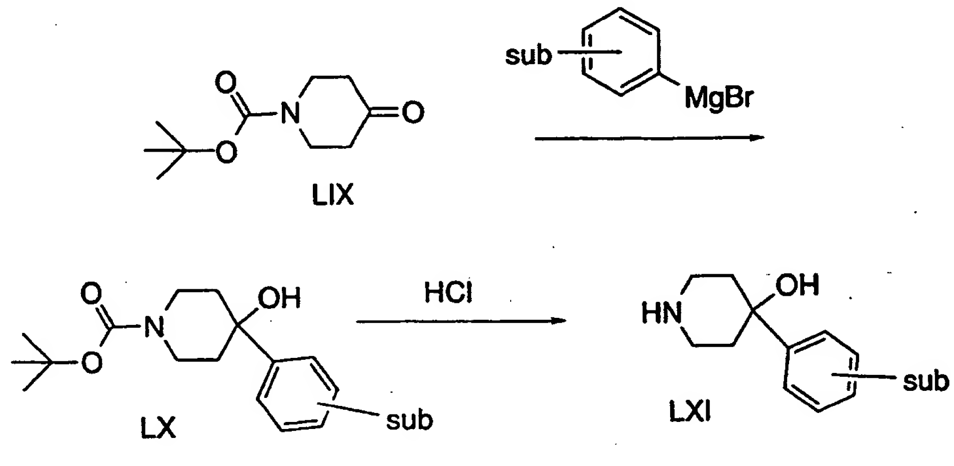


Cu(I)I
CO_2CH_3
N
Cl
1. H_2, Pt_2O
2. $(Boc)_2O$
O
N
O
H
Br
sub
NaHMDS
1. HCl, EtOAc
2. iPr_2NEt
R^8
Cl

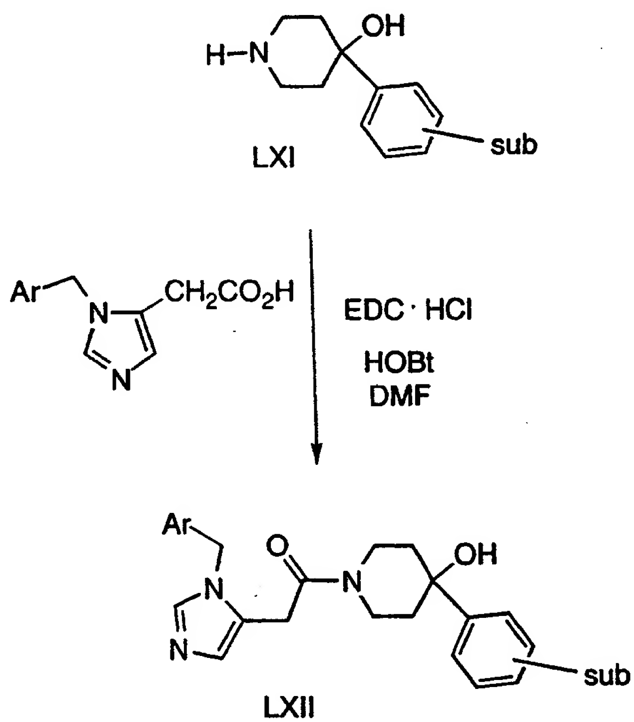
SCHEME 23



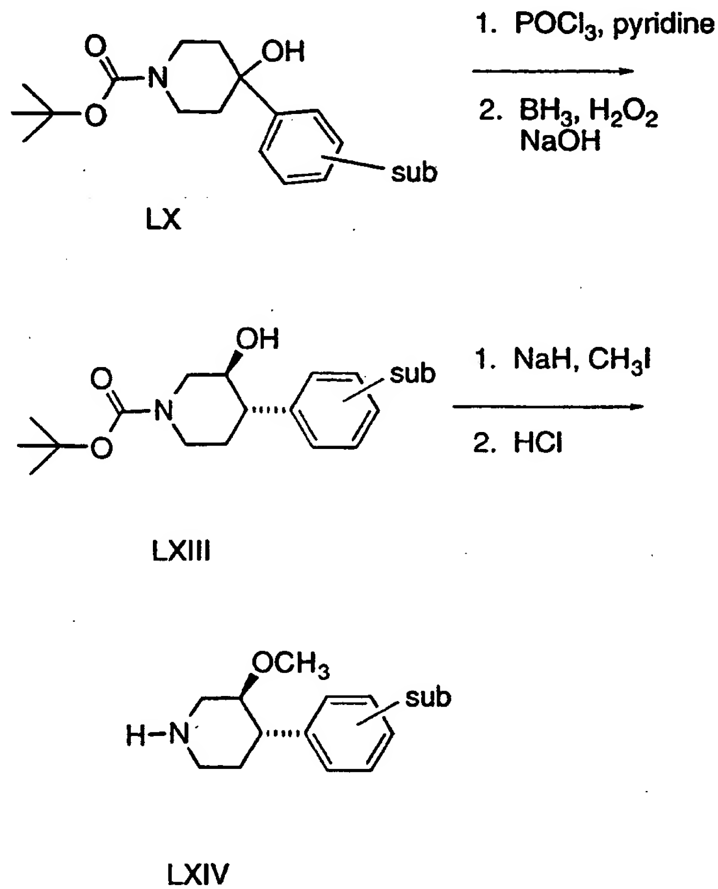
SCHEME 24



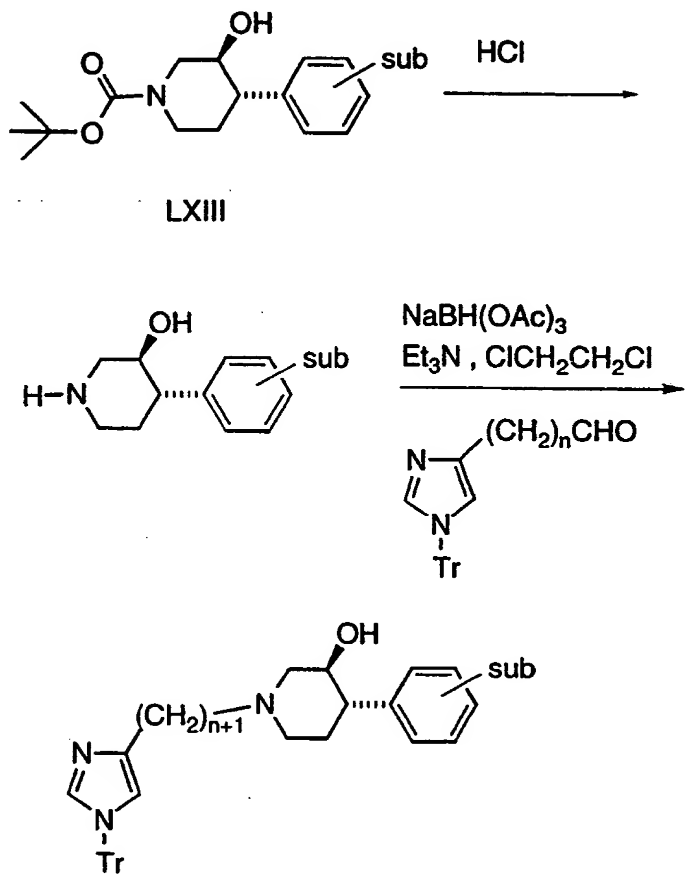
SCHEME 25



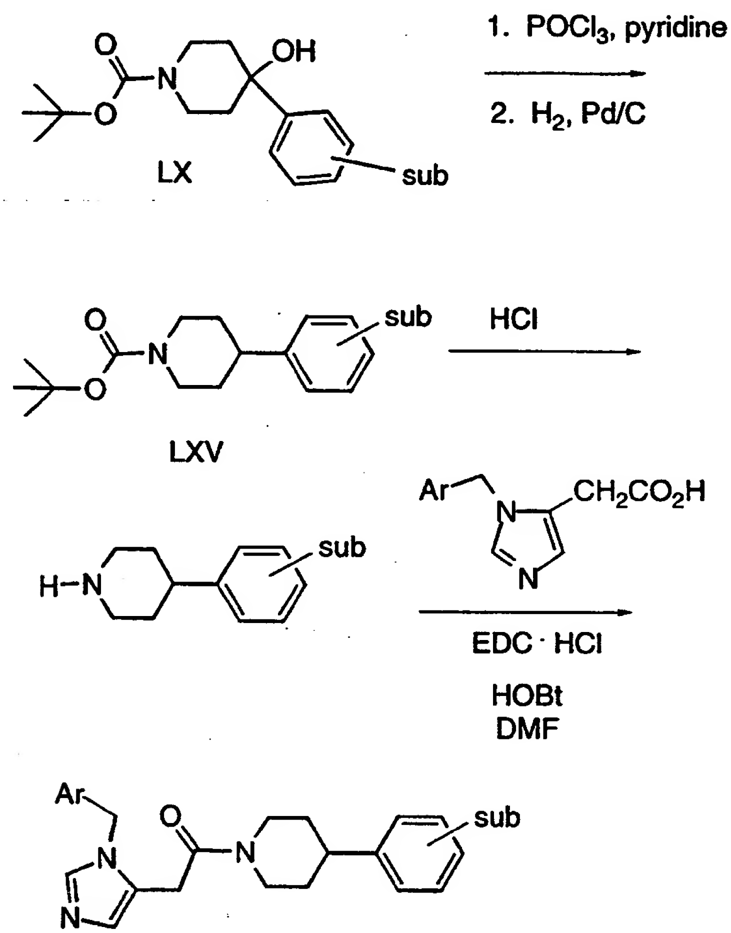
SCHEME 26


1. $POCl_3$, pyridine
2. BH_3, H_2O_2
NaOH
OH
sub
LX
1. NaH, CH_3I
2. HCl
OH
sub
LXIII
OCH_3
sub
H–N
LXIV

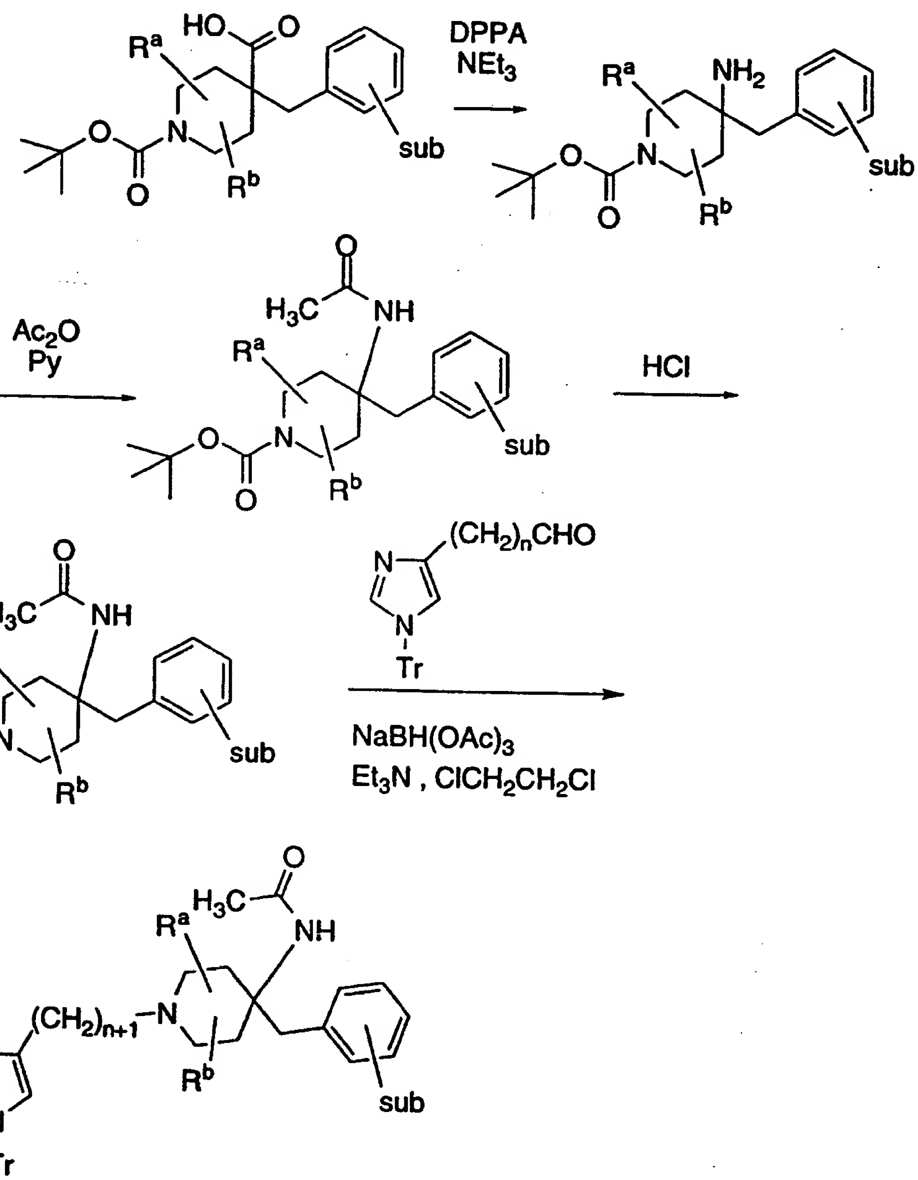
SCHEME 27


OH
sub
HCl
LXIII
OH
sub
H–N
NaBH(OAc)3
Et3N , ClCH2CH2Cl
(CH2)nCHO
N
N
Tr
OH
sub
(CH2)n+1
N
N
N
Tr

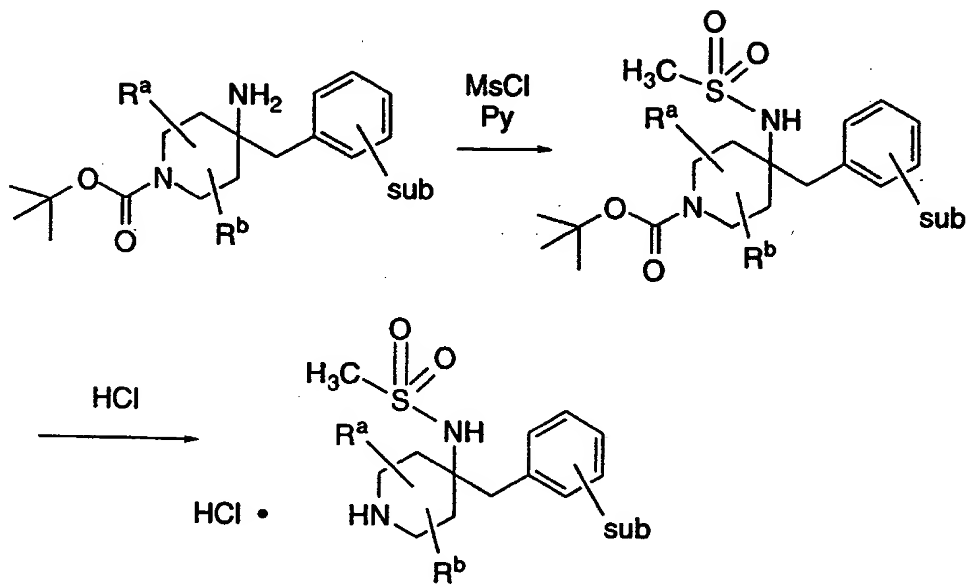
SCHEME 28


LX
OH
sub
1. $POCl_3$, pyridine
2. H_2, Pd/C
LXV
HCl
CH_2CO_2H
EDC · HCl
HOBt
DMF

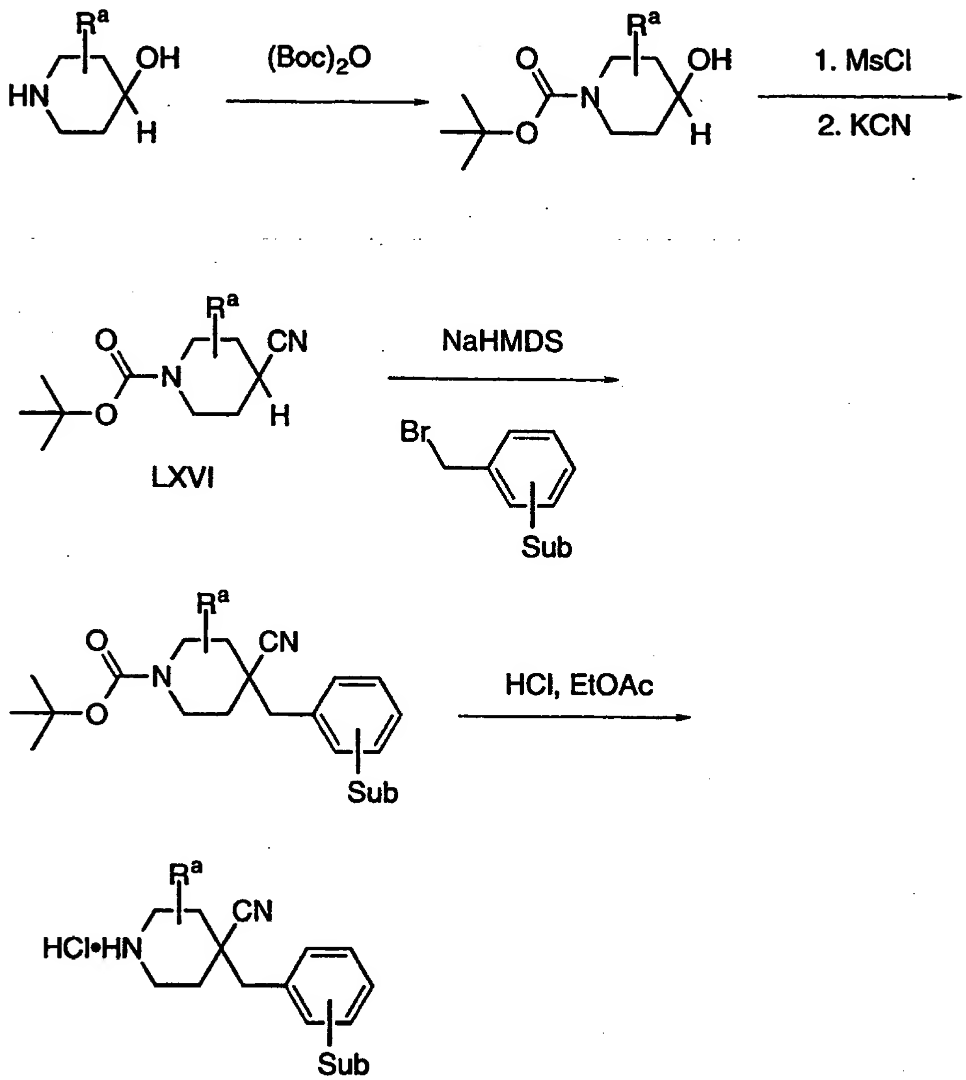
SCHEME 29 (continued)



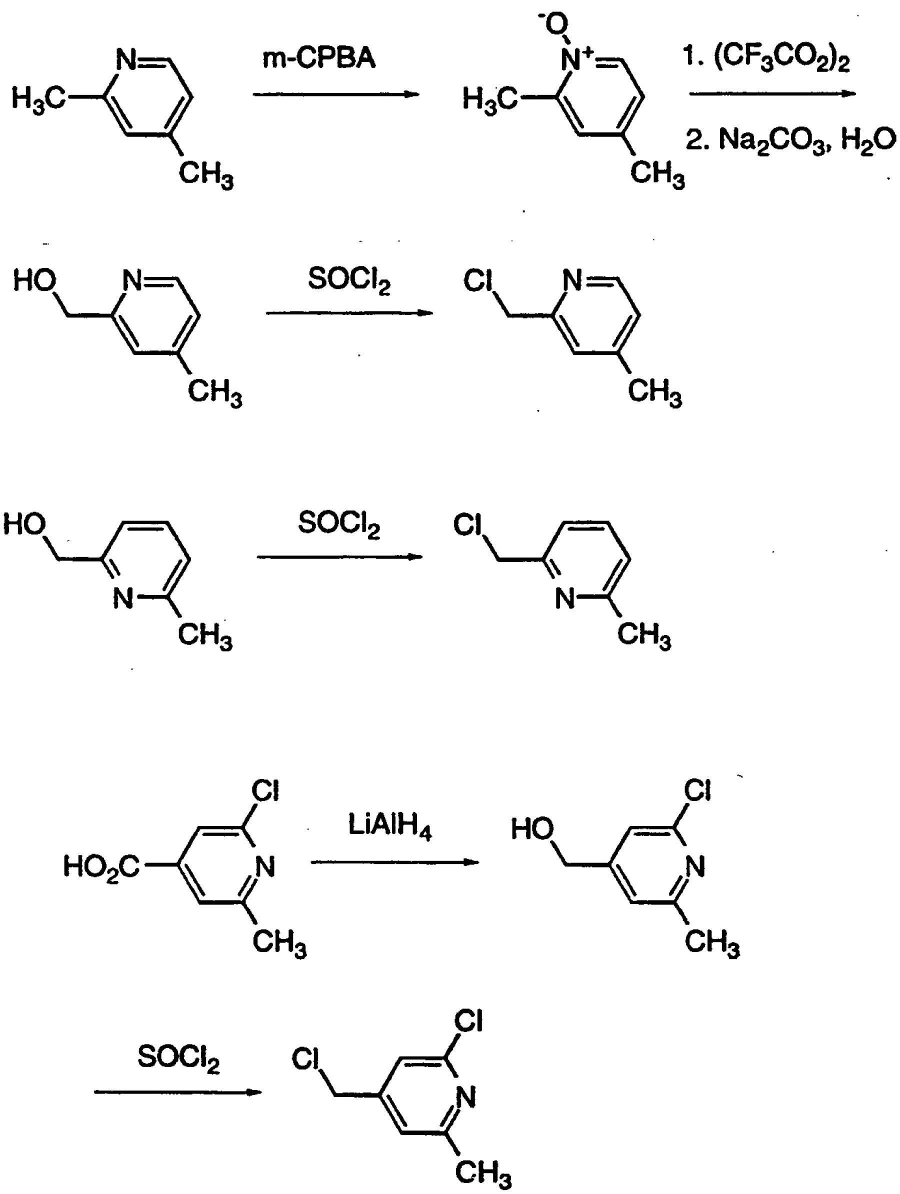
SCHEME 30



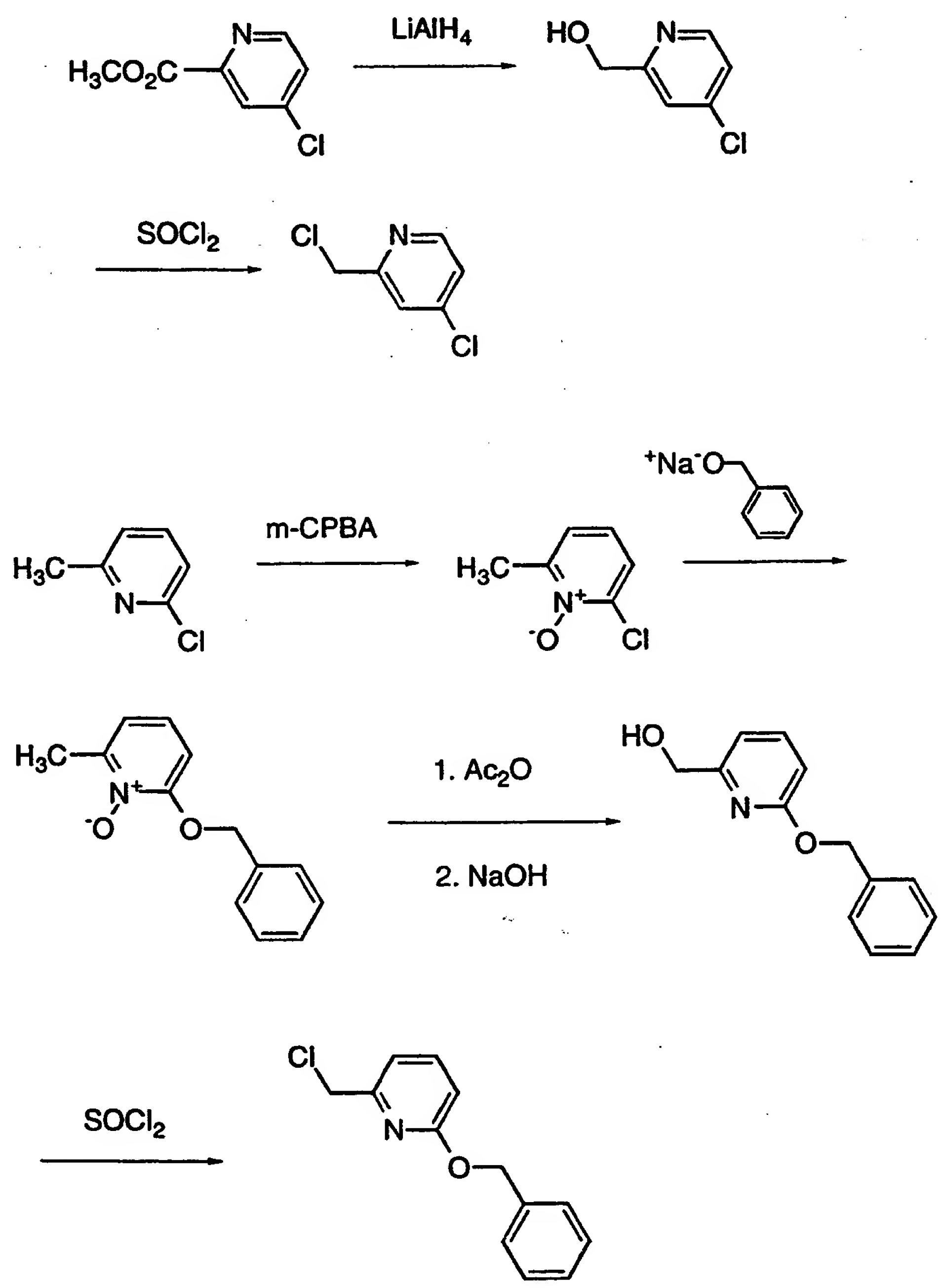
SCHEME 31



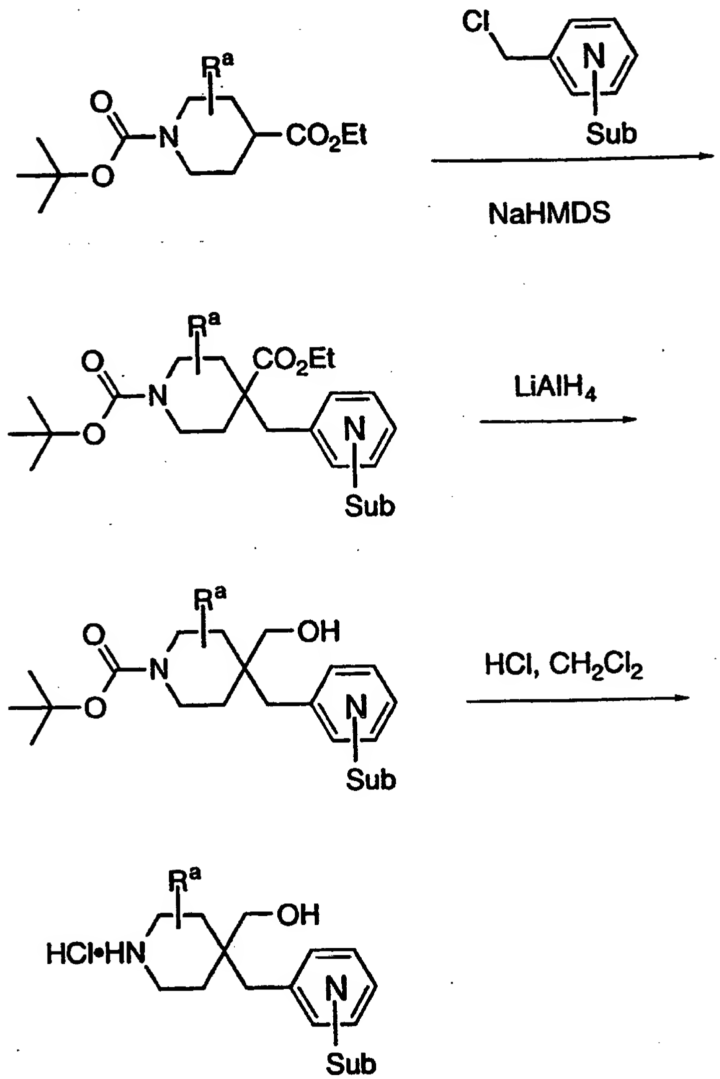
SCHEME 32



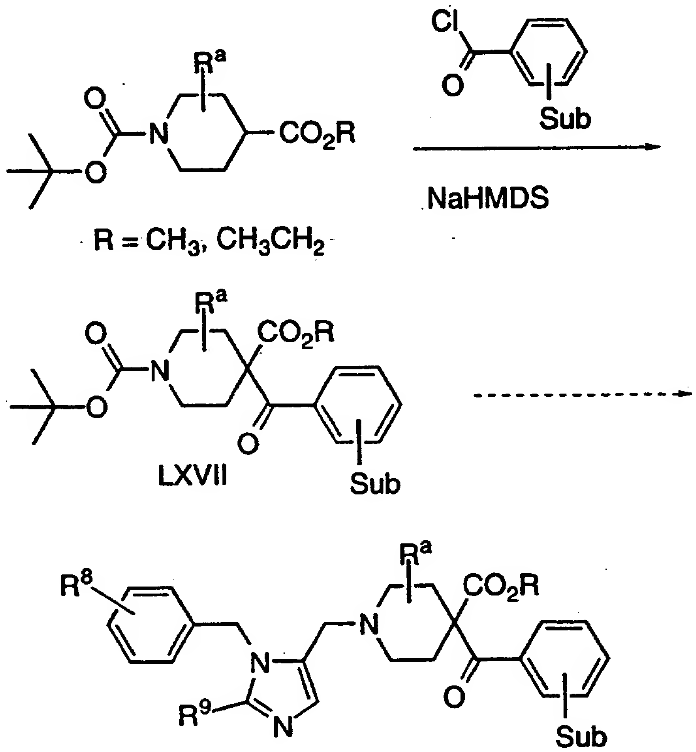
SCHEME 32 (continued)



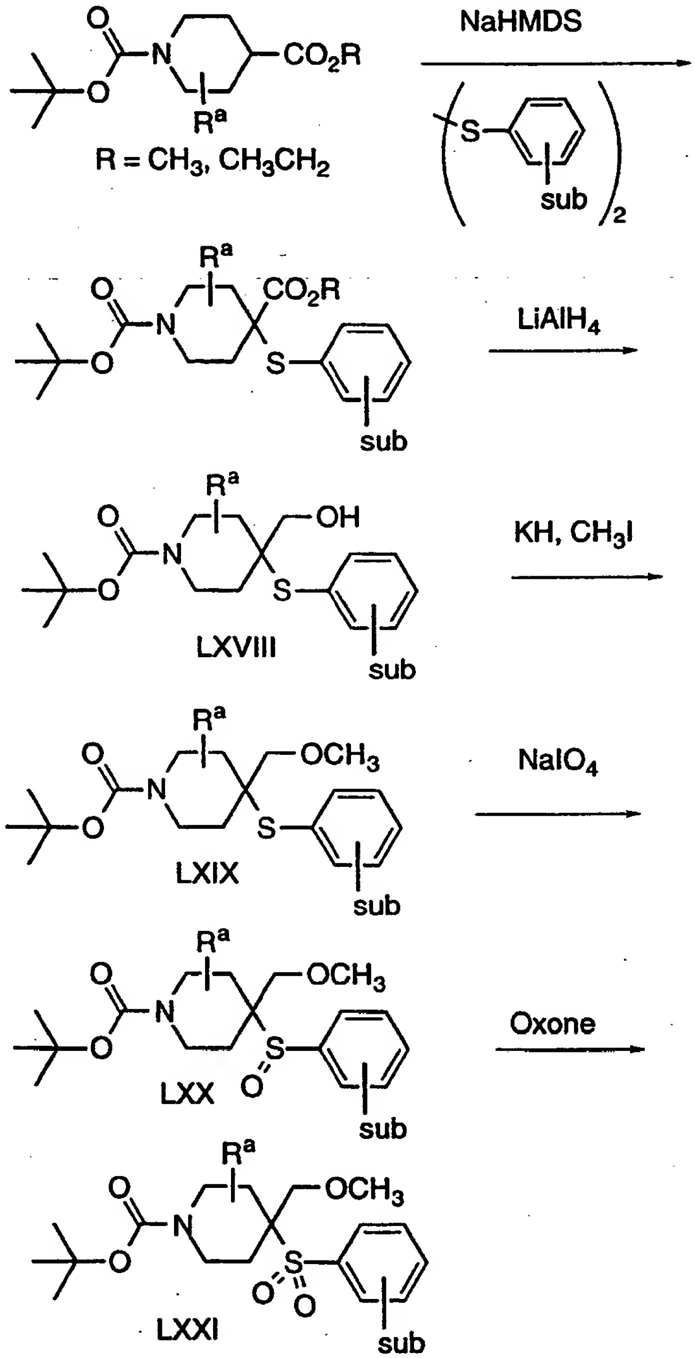
SCHEME 33



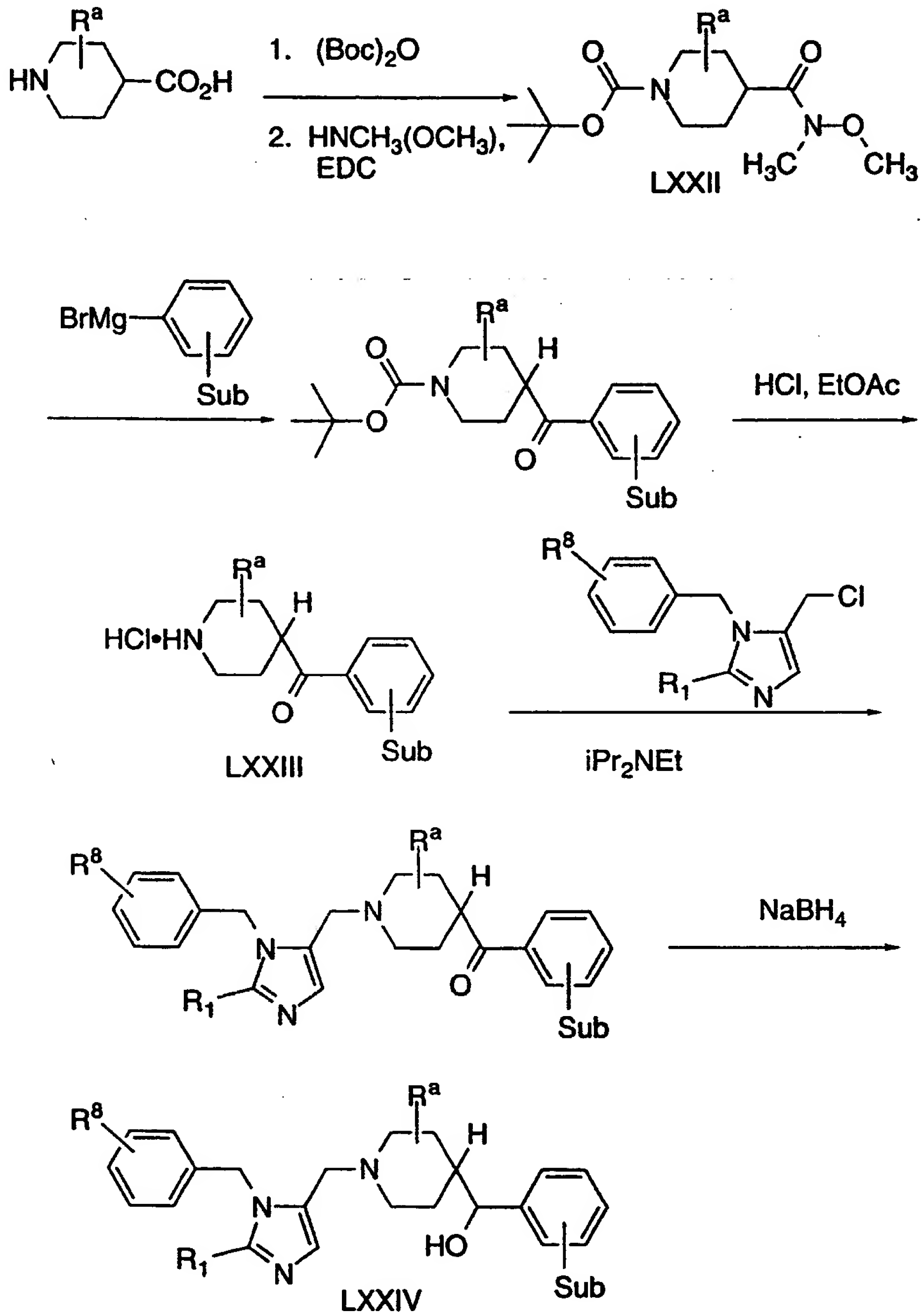
SCHEME 34



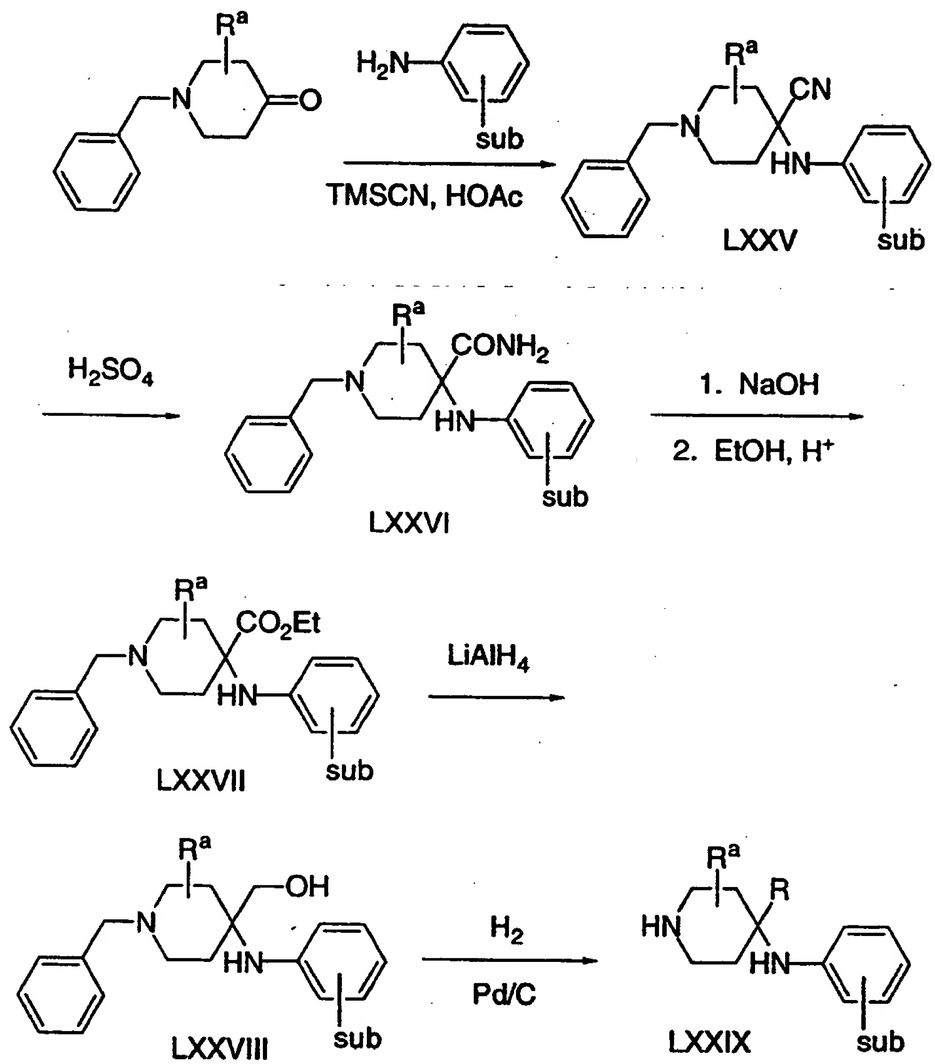
SCHEME 35


NaHMDS
R = CH_3, CH_3CH_2
CO$_2$R
R^a
sub
LiAlH$_4$
KH, CH$_3$I
OH
LXVIII
NaIO$_4$
OCH$_3$
LXIX
Oxone
LXX
LXXI

SCHEME 36


Ra
HN
CO2H
1. (Boc)2O
2. HNCH3(OCH3), EDC
O
N
O
N
O
H3C
CH3
LXXII
BrMg
Sub
H
HCl, EtOAc
HCl•HN
LXXIII
R8
Cl
R1
iPr2NEt
NaBH4
HO
LXXIV

SCHEME 37



Compounds of this invention of formula (III) are prepared by employing the reactions shown in the following Reaction Schemes 38-51, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Some key bond-forming and peptide modifying reactions are:

Reaction A Amide bond formation and protecting group cleavage using standard solution or solid phase methodologies.

Reaction B Preparation of a reduced peptide subunit by reductive alkylation of an amine by an aldehyde using sodium cyanoborohydride or other reducing agents.

Reaction C Alkylation of a reduced peptide subunit with an alkyl or aralkyl halide or, alternatively, reductive alkylation of a reduced peptide subunit with an aldehyde using sodium cyanoborohydride or other reducing agents.

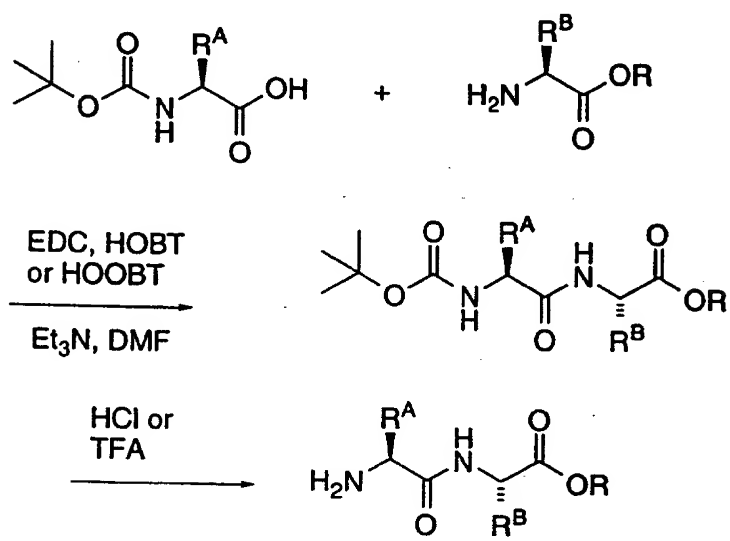
Reaction D Peptide bond formation and protecting group cleavage using standard solution or solid phase methodologies.

Reaction E Preparation of a reduced subunit by borane reduction of the amide moiety.

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Reaction Schemes and in Reaction Schemes 43-51 hereinbelow.

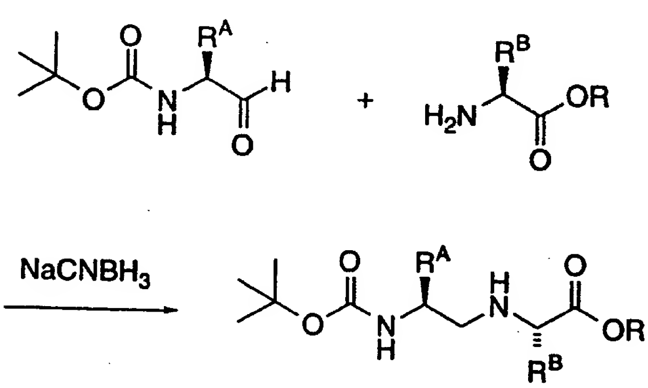
REACTION SCHEME 38

Reaction A. Coupling of residues to form an amide bond



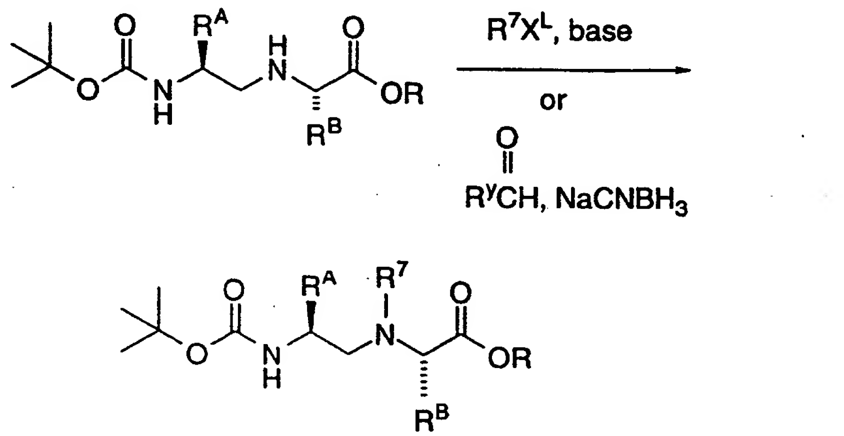
REACTION SCHEME 39

Reaction B. Preparation of reduced peptide subunits by reductive alkylation



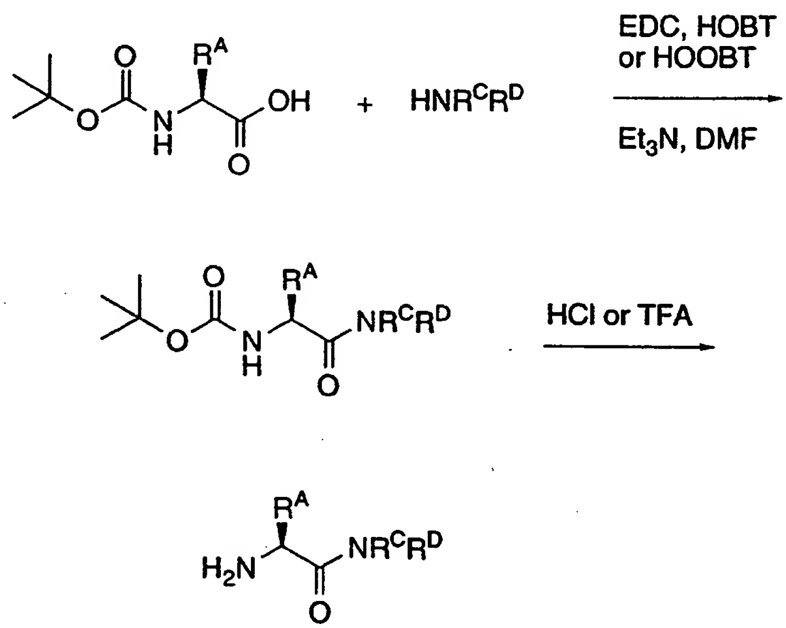
REACTION SCHEME 40

Reaction C. Alkylation/reductive alkylation of reduced peptide subunits



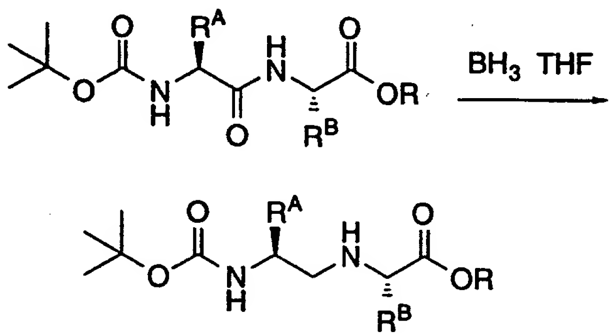
REACTION SCHEME 41

Reaction D. Coupling of residues to form an amide bond



REACTION SCHEME 42

Reaction E. Preparation of reduced dipeptides from peptides



where RA and RB are R2, R3 or R5 as previously defined; RC and RD are R^7 or R^{12}; XL is a leaving group, e.g., Br^-, I^- or MsO^-; and Ry is defined such that R^7 is generated by the reductive alkylation process.

In addition to the reactions described in Reaction Schemes 26-30, other reactions used to generate the compounds of formula (III) of this invention are shown in the Reaction Schemes 43-51. All of the substituents shown in the Reaction Schemes, represent the same substituents as defined hereinabove. The substituent "Ar" in the Reaction Schemes represents a carbocyclic or heterocyclic, substituted or unsubstituted aromatic ring.

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Reaction Schemes. The sequential order whereby substituents are incorporated into the compounds is often not critical and thus the order of reactions described in the Reaction Schemes are illustrative only and are not limiting.

Synopsis of Reaction Schemes 43-51:

The requisite intermediates are in some cases commercially available, or can be readily prepared according to known literature

procedures, including those described in Reaction Schemes 38-42 hereinabove.

Reaction Scheme 43 illustrates incorporation of the cyclic amine moiety, such as a reduced prolyl moiety, into the compounds of the formula III of the instant invention. Reduction of the azide LXXXI provides the amine LXXXII, which may be mono- or di-substituted using techniques described above. As an example, incorporation of a naphthylmethyl group and an acetyl group is illustrated.

As shown in Reaction Scheme 44, direct attachment of a aromatic ring to a substituted amine such as LXXXIII is accomplished by coupling with a triarylbismuth reagent, such as tris(3-chlorophenyl) bismuth.

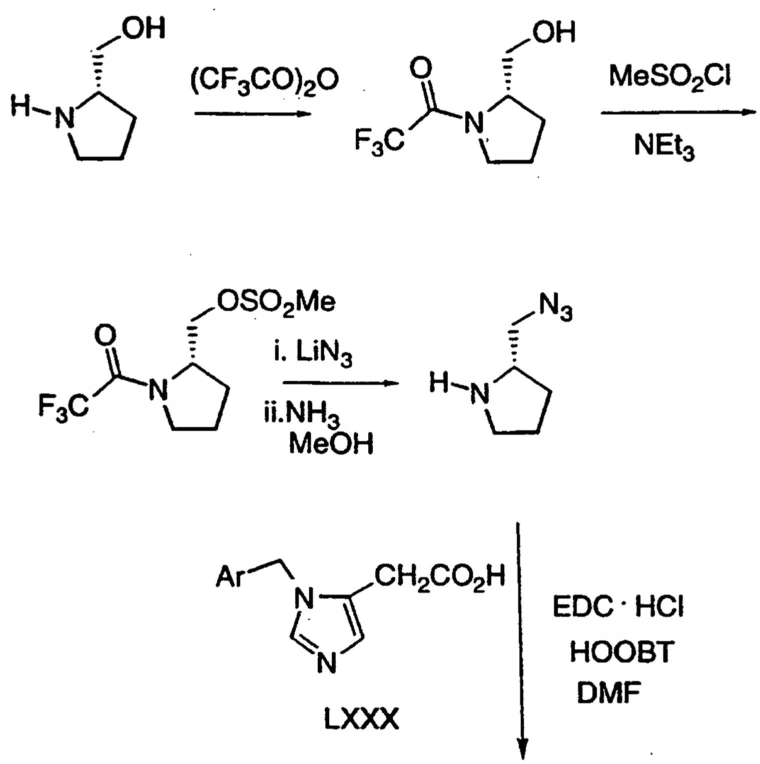
Reaction Scheme 45 illustrates the use of protecting groups to prepare compounds of the instant invention wherein the cyclic amine contains an alkoxy moiety. The hydroxy moiety of key intermediate LXXXIVa may be further converted to a fluoro or phenoxy moiety, as shown in Reaction Scheme 46. Intermediates LXXXV and LXXXVI may then be further elaborated to provide the instant compounds.

Reaction Scheme 474 illustrates syntheses of instant compounds wherein the variable $-(CR^4{}_2)_qA^3(CR^5{}_2)_nR^6$ is a suitably substituted α-hydroxybenzyl moiety. Thus the protected intermediate aldehyde is treated with a suitably substituted phenyl Grignard reagent to provide the enantiomeric mixture LXXXVII. Treatment of the mixture with 2-picolinyl chloride allows chromatographic resolution of compounds LXXXVIII and IXC. Removal of the picolinoyl group followed by deprotection provides the optically pure intermediate XC which can be further processed as described hereinabove to yield the instant compounds.

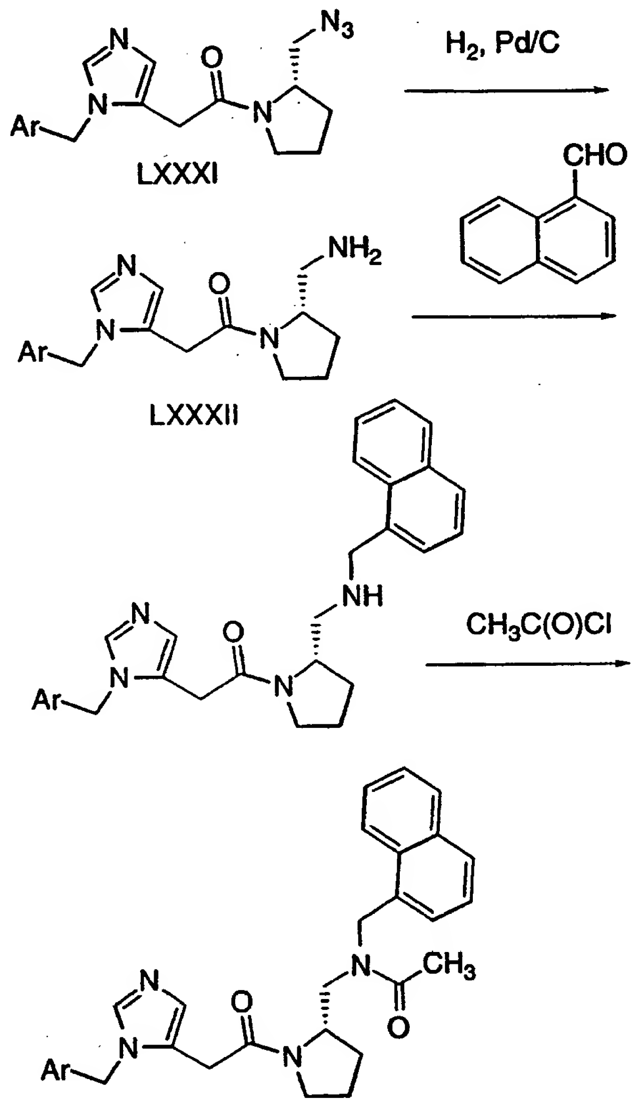
Syntheses of imidazole-containing intermediates useful in synthesis of instant compounds wherein the variable p is 0 or 1 and Z is H_2 are shown in Reaction Scheme 48 and 49. Thus the mesylate XCI can be utilized to alkylate a suitably substituted amine or cyclic amine, while aldehyde XCII can be used to similarly reductively alkylate such an amine.

Reaction Scheme 50 illustrates the syntheses of imidazole-containing intermediates wherein the attachment point of the $-(CR^2{}_2)_p$-C(Z)- moiety to W (imidazolyl) is through an imidazole ring nitrogen. Reaction Scheme 51 illustrates the synthesis of an intermediate wherein an R^2 substituent is a methyl.

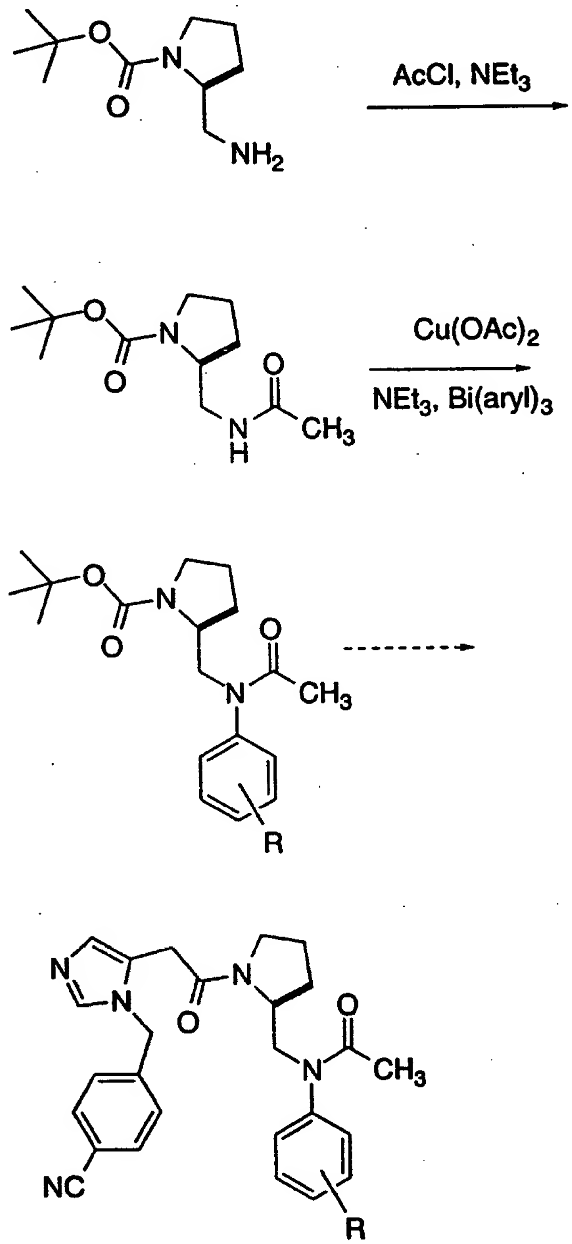
REACTION SCHEME 43



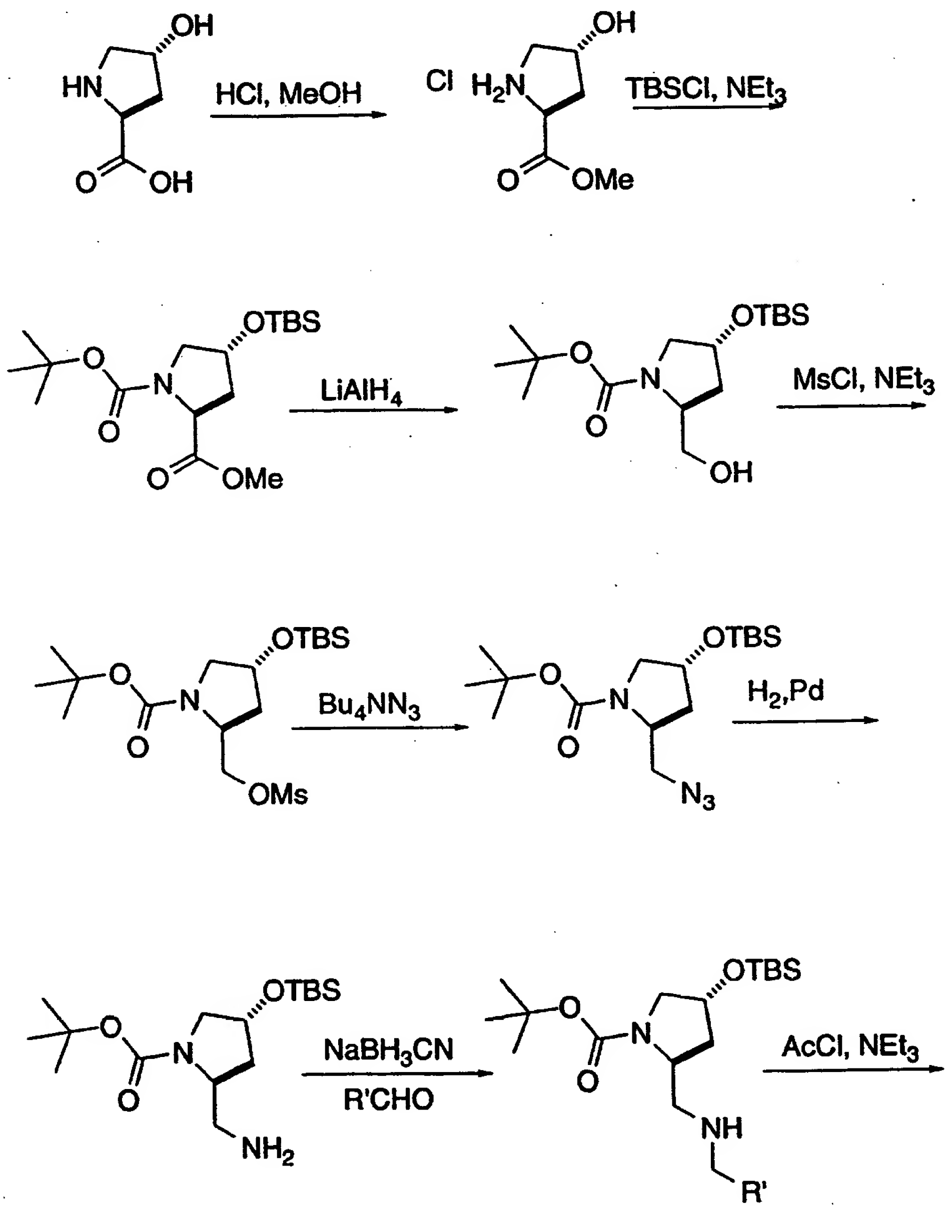
REACTION SCHEME 43 (continued)



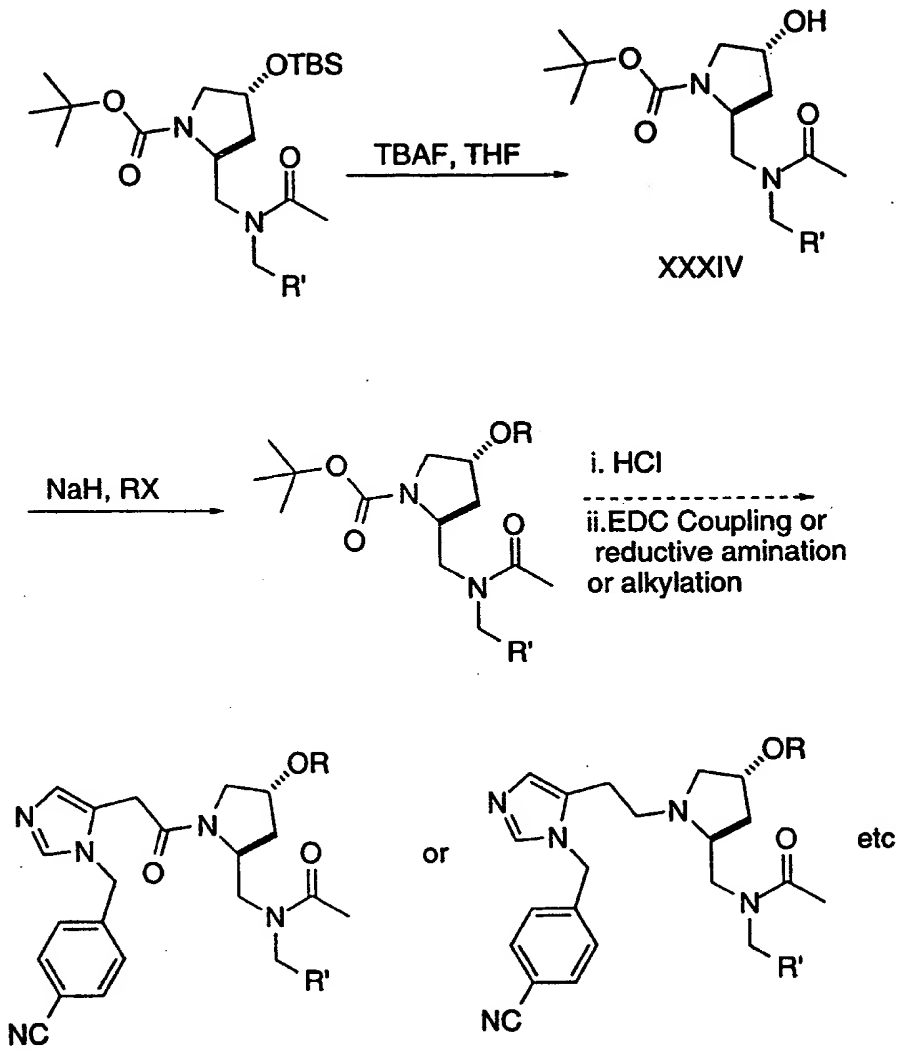
REACTION SCHEME 44



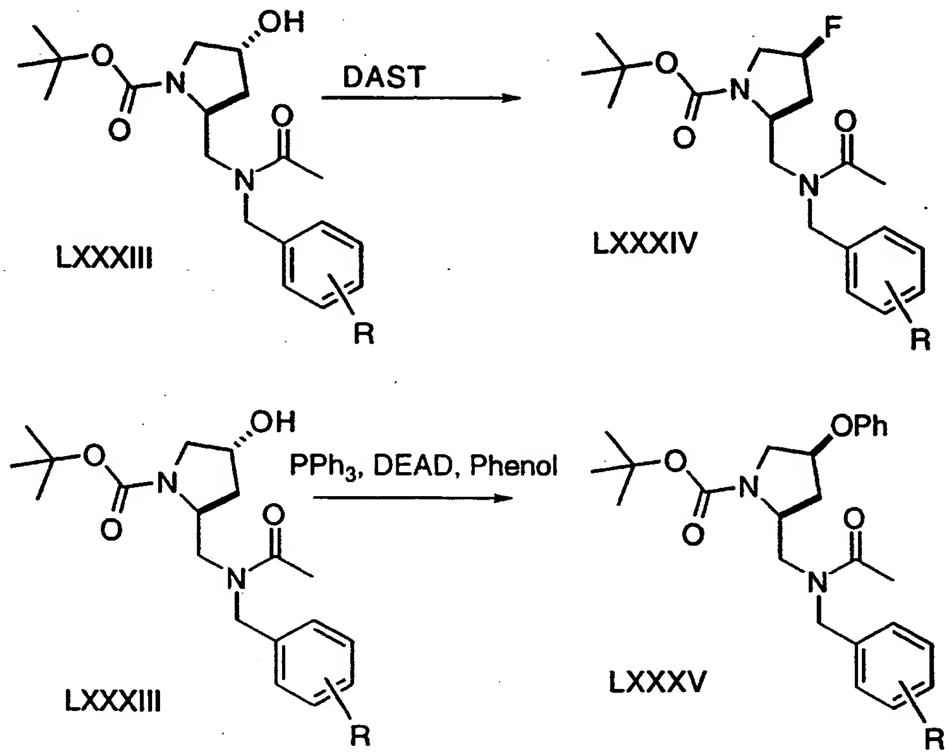
REACTION SCHEME 45



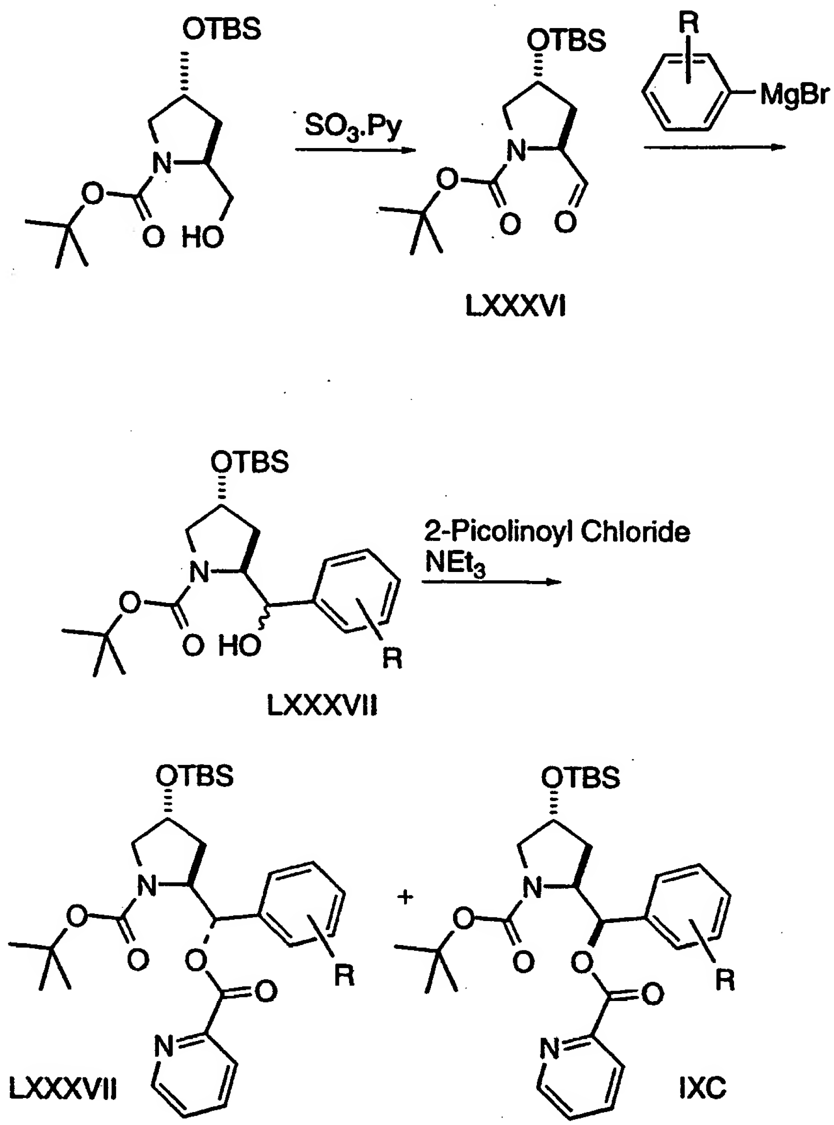
REACTION SCHEME 45 (continued)



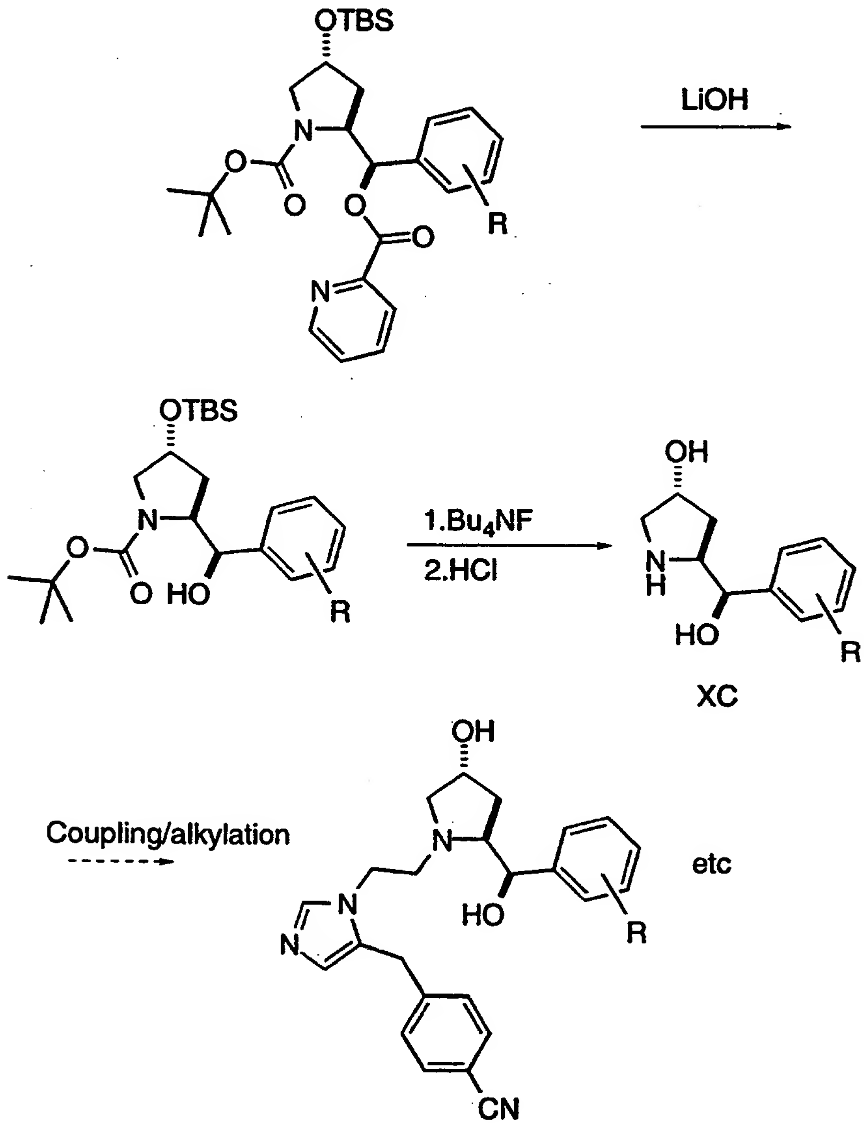
REACTION SCHEME 46



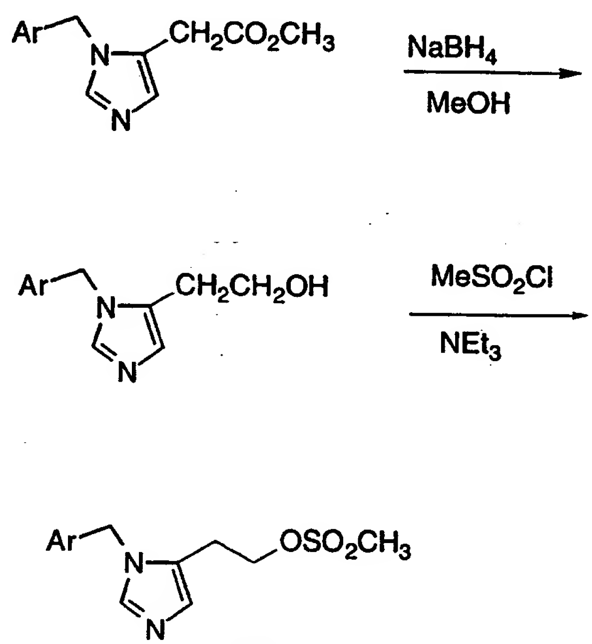
REACTION SCHEME 47



REACTION SCHEME 47 (continued)

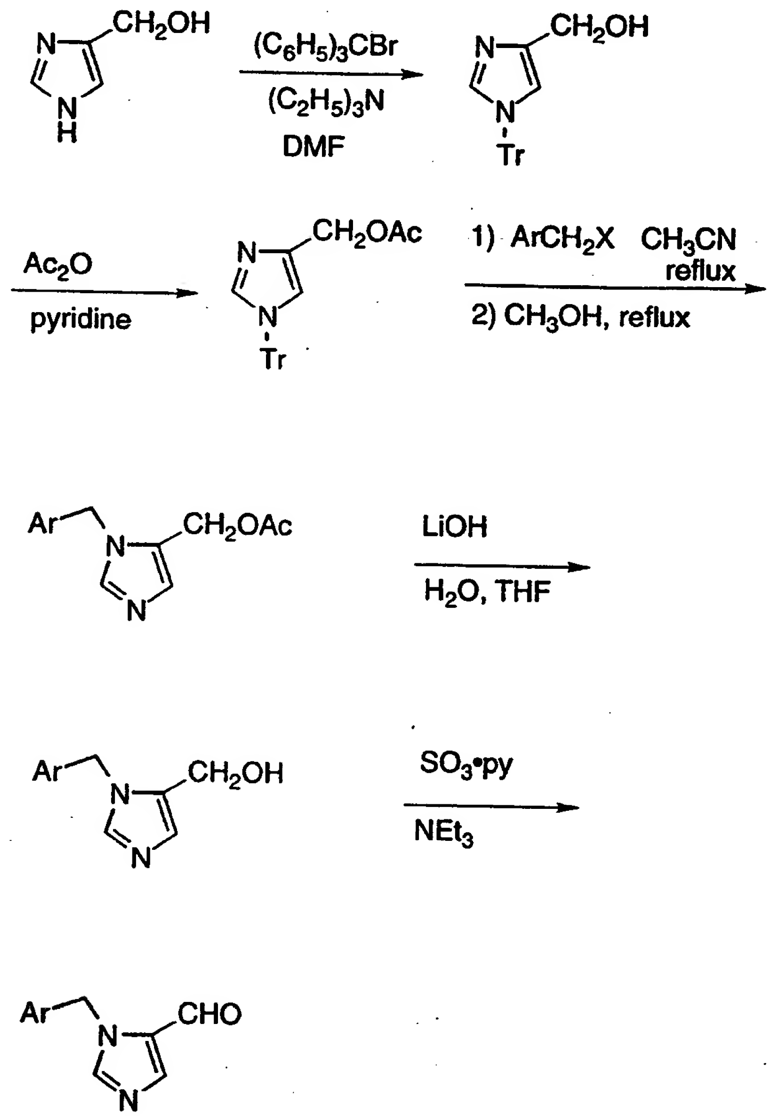


REACTION SCHEME 48



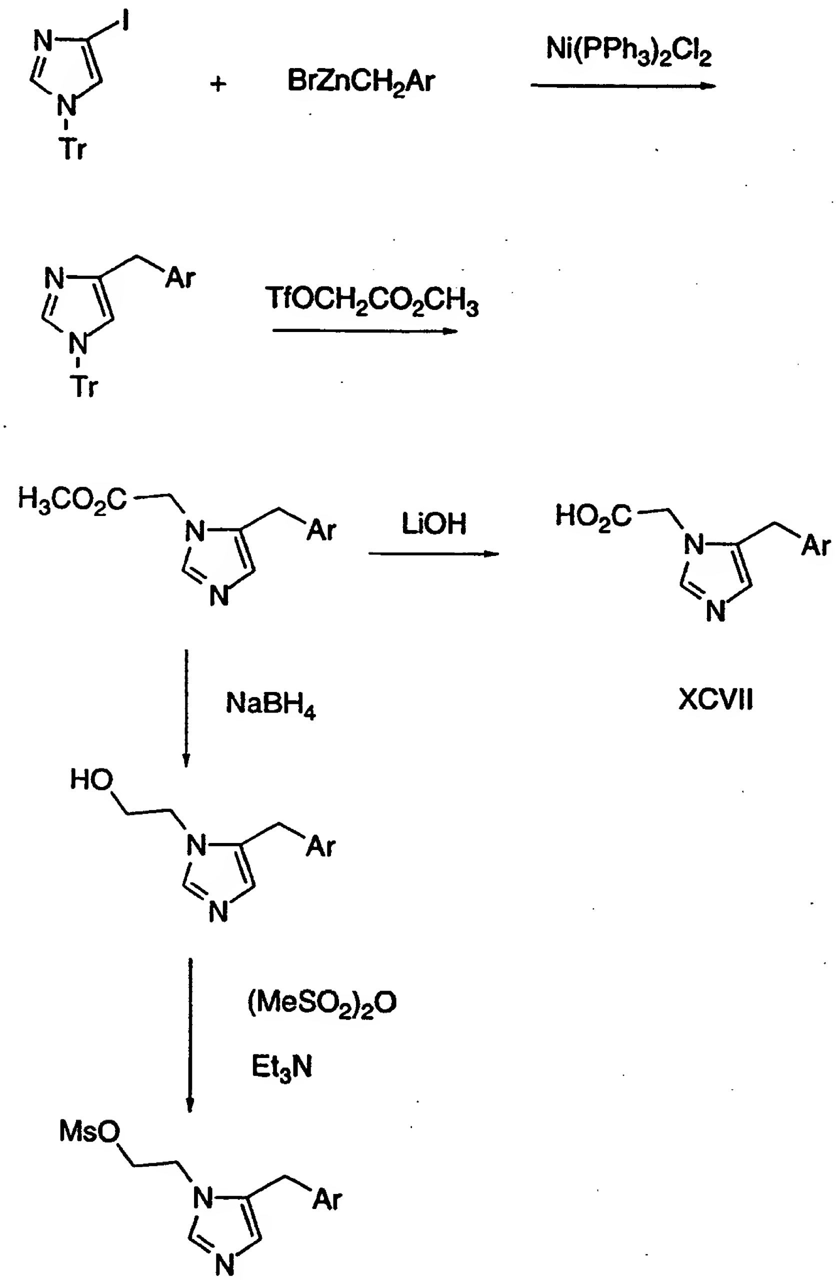
XCl

REACTION SCHEME 49



XCII

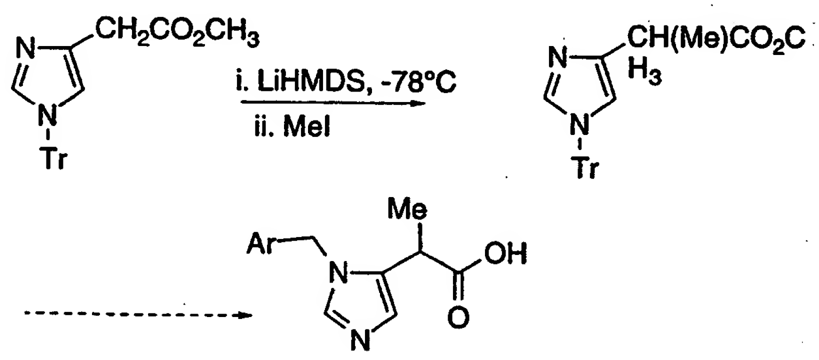
REACTION SCHEME 50



XCVII

XCVIII

REACTION SCHEME 51



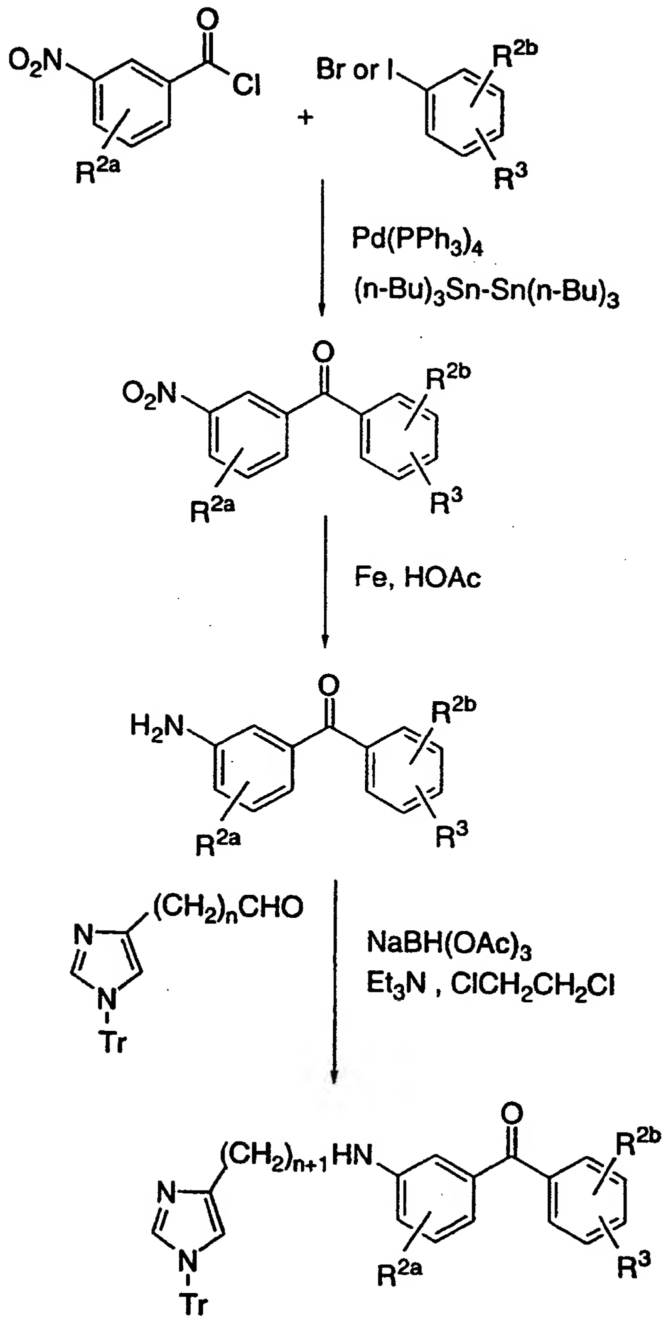
XCVI

The prenyl transferase inhibitors of formula (A) can be synthesized in accordance with Reaction Scheme below, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Some key reactions utilized to form the aminodiphenyl moiety of the instant compounds are shown.

The reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Reaction Scheme.

A method of forming the benzophenone intermediates, illustrated in Reaction Scheme 52, is a Stille reaction with an aryl stannane. Such amine intermediates may then be reacted as illustrated hereinabove with a variety of aldehydes and esters/acids.

REACTION SCHEME 52



EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof.

The standard workup referred to in the examples refers to solvent extraction and washing the organic solution with 10% citric acid, 10% sodium bicarbonate and brine as appropriate. Solutions were dried over sodium sulfate and evaporated *in vacuo* on a rotary evaporator.

EXAMPLES 1

1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)imidazolylmethyl]-2-piperazinone dihydrochloride (Compound 1)

Step A: Preparation of 1-triphenylmethyl-4-(hydroxymethyl)-imidazole

To a solution of 4-(hydroxymethyl)imidazole hydrochloride (35.0 g, 260 mmol) in 250 mL of dry DMF at room temperature was added triethylamine (90.6 mL, 650 mmol). A white solid precipitated from the solution. Chlorotriphenylmethane (76.1 g, 273 mmol) in 500 mL of DMF was added dropwise. The reaction mixture was stirred for 20 hours, poured over ice, filtered, and washed with ice water. The resulting product was slurried with cold dioxane, filtered, and dried *in vacuo* to provide the titled product as a white solid which was sufficiently pure for use in the next step.

Step B: Preparation of 1-triphenylmethyl-4-(acetoxymethyl)-imidazole

Alcohol from Step A (260 mmol, prepared above) was suspended in 500 mL of pyridine. Acetic anhydride (74 mL, 780 mmol) was added dropwise, and the reaction was stirred for

48 hours during which it became homogeneous. The solution was poured into 2 L of EtOAc, washed with water (3 x 1 L), 5% aq. HCl soln. (2 x 1 L), sat. aq. $NaHCO_3$, and brine, then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product. The acetate was isolated as a white powder which was sufficiently pure for use in the next reaction.

Step C: Preparation of 1-(4-cyanobenzyl)-5-(acetoxymethyl)-imidazole hydrobromide

A solution of the product from Step B (85.8 g, 225 mmol) and α-bromo-*p*-tolunitrile (50.1 g, 232 mmol) in 500 mL of EtOAc was stirred at 60°C for 20 hours, during which a pale yellow precipitate formed. The reaction was cooled to room temperature and filtered to provide the solid imidazolium bromide salt. The filtrate was concentrated *in vacuo* to a volume 200 mL, reheated at 60°C for two hours, cooled to room temperature, and filtered again. The filtrate was concentrated *in vacuo* to a volume 100 mL, reheated at 60°C for another two hours, cooled to room temperature, and concentrated *in vacuo* to provide a pale yellow solid. All of the solid material was combined, dissolved in 500 mL of methanol, and warmed to 60°C. After two hours, the solution was reconcentrated *in vacuo* to provide a white solid which was triturated with hexane to remove soluble materials. Removal of residual solvents *in vacuo* provided the titled product hydrobromide as a white solid which was used in the next step without further purification.

Step D: Preparation of 1-(4-cyanobenzyl)-5-(hydroxymethyl)-imidazole

To a solution of the acetate from Step C (50.4 g, 150 mmol) in 1.5 L of 3:1 THF/water at 0°C was added lithium hydroxide monohydrate (18.9 g, 450 mmol). After one hour, the reaction was concentrated *in vacuo*, diluted with EtOAc (3 L), and washed with water, sat. aq. $NaHCO_3$ and brine. The solution was then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide

the crude product as a pale yellow fluffy solid which was sufficiently pure for use in the next step without further purification.

Step E: Preparation of 1-(4-cyanobenzyl)-5-imidazolecarboxaldehyde

To a solution of the alcohol from Step D (21.5 g, 101 mmol) in 500 mL of DMSO at room temperature was added triethylamine (56 mL, 402 mmol), then SO_3-pyridine complex (40.5 g, 254 mmol). After 45 minutes, the reaction was poured into 2.5 L of EtOAc, washed with water (4 x 1 L) and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the aldehyde as a white powder which was sufficiently pure for use in the next step without further purification.

Step F: Preparation of N-(3-chlorophenyl)ethylenediamine hydrochloride

To a solution of 3-chloroaniline (30.0 mL, 284 mmol) in 500 mL of dichloromethane at 0°C was added dropwise a solution of 4 N HCl in 1,4-dioxane (80 mL, 320 mmol HCl). The solution was warmed to room temperature, then concentrated to dryness *in vacuo* to provide a white powder. A mixture of this powder with 2-oxazolidinone (24.6 g, 282 mmol) was heated under nitrogen atmosphere at 160°C for 10 hours, during which the solids melted, and gas evolution was observed. The reaction was allowed to cool, forming the crude diamine hydrochloride salt as a pale brown solid.

Step G: Preparation of *N*-(*tert*-butoxycarbonyl)-*N'*-(3-chlorophenyl)ethylenediamine

The amine hydrochloride from Step F (*ca.* 282 mmol, crude material prepared above) was taken up in 500 mL of THF and 500 mL of sat. aq. $NaHCO_3$ soln., cooled to 0°C, and di-*tert*-butylpyrocarbonate (61.6 g, 282 mmol) was added. After 30 h, the reaction was poured into EtOAc, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the titled

carbamate as a brown oil which was used in the next step without further purification.

Step H: Preparation of *N*-[2-(*tert*-butoxycarbamoyl)ethyl]-*N*-(3-chlorophenyl)-2-chloroacetamide

A solution of the product from Step G (77 g, *ca.* 282 mmol) and triethylamine (67 mL, 480 mmol) in 500 mL of CH_2Cl_2 was cooled to 0°C. Chloroacetyl chloride (25.5 mL, 320 mmol) was added dropwise, and the reaction was maintained at 0°C with stirring. After 3 h, another portion of chloroacetyl chloride (3.0 mL) was added dropwise. After 30 min, the reaction was poured into EtOAc (2 L) and washed with water, sat. aq. NH_4Cl soln, sat. aq. $NaHCO_3$ soln., and brine. The solution was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the chloroacetamide as a brown oil which was used in the next step without further purification.

Step I: Preparation of 4-(*tert*-butoxycarbonyl)-1-(3-chlorophenyl)-2-piperazinone

To a solution of the chloroacetamide from Step H (*ca.* 282 mmol) in 700 mL of dry DMF was added K_2CO_3 (88 g, 0.64 mol). The solution was heated in an oil bath at 70-75°C for 20 hrs., cooled to room temperature, and concentrated *in vacuo* to remove *ca.* 500 mL of DMF. The remaining material was poured into 33% EtOAc/hexane, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the product as a brown oil. This material was purified by silica gel chromatography (25-50% EtOAc/hexane) to yield pure product, along with a sample of product (ca. 65% pure by HPLC) containing a less polar impurity.

Step J: Preparation of 1-(3-chlorophenyl)-2-piperazinone

Through a solution of Boc-protected piperazinone from Step I (17.19 g, 55.4 mmol) in 500 mL of EtOAc at -78°C was bubbled anhydrous HCl gas. The saturated solution was warmed to

0°C, and stirred for 12 hours. Nitrogen gas was bubbled through the reaction to remove excess HCl, and the mixture was warmed to room temperature. The solution was concentrated *in vacuo* to provide the hydrochloride as a white powder. This material was taken up in 300 mL of CH_2Cl_2 and treated with dilute aqueous $NaHCO_3$ solution. The aqueous phase was extracted with CH_2Cl_2 (8 x 300 mL) until tlc analysis indicated complete extraction. The combined organic mixture was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the titled free amine as a pale brown oil.

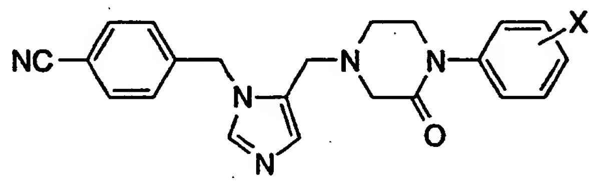
Step K: Preparation of 1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)imidazolylmethyl]-2-piperazinone dihydrochloride

To a solution of the amine from Step J (55.4 mmol, prepared above) in 200 mL of 1,2-dichloroethane at 0°C was added 4Å powdered molecular sieves (10 g), followed by sodium triacetoxyborohydride (17.7 g, 83.3 mmol). The imidazole carboxaldehyde from Step E of Example 1 (11.9 g, 56.4 mmol) was added, and the reaction was stirred at 0°C. After 26 hours, the reaction was poured into EtOAc, washed with dilute aq. $NaHCO_3$, and the aqueous layer was back-extracted with EtOAc. The combined organics were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting product was taken up in 500 mL of 5:1 benzene:CH_2Cl_2, and propylamine (20 mL) was added. The mixture was stirred for 12 hours, then concentrated *in vacuo* to afford a pale yellow foam. This material was purified by silica gel chromatography (2-7% MeOH/CH_2Cl_2), and the resultant white foam was taken up in CH_2Cl_2 and treated with 2.1 equivalents of 1 M HCl/ether solution. After concentrated *in vacuo*, the product dihydrochloride was isolated as a white powder.

Examples 2-5 (Table 1) were prepared using the above protocol, which describes the synthesis of the structurally related compound

1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-imidazolylmethyl]-2-piperazinone dihydrochloride. In Step F, the appropriately substituted aniline was used in place of 3-chloroaniline.

Table 1: 1-Aryl-4-[1-(4-cyanobenzyl)imidazolylmethyl]-2-piperazinones



Example	X	FAB mass spectrum (M+1)	CHN Analysis
2	3-OCF_3	456	$C_{23}H_{20}F_3N_5O_2$•2.0HCl•0.60H_2O calcd; C, 51.24; H, 4.34; N, 12.99. found; C, 51.31; H, 4.33; N, 12.94.
3	2,5-$(CH_3)_2$	400	$C_{24}H_{25}N_5O$•2.00HCl•0.65H_2O calcd; C, 59.54; H, 5.89; N, 14.47 found; C, 59.54; H, 5.95; N, 14.12.
4	3-CH_3	386	$C_{23}H_{23}N_5O$•2.0HCl•0.80H_2O calcd; C, 58.43; H, 5.67; N, 14.81. found; C, 58.67; H, 6.00; N, 14.23.
5	3-I	498	$C_{22}H_{20}N_5OI$•2.25HCl•0.90H_2O calcd; C, 44.36; H, 4.07; N, 11.76. found; C, 44.37; H, 4.06; N, 11.42.

EXAMPLE 6

1-(3-chlorophenyl)-4-[1-(4-cyano-3-methoxybenzyl)imidazolylmethyl]-2-piperazinone dihydrochloride

Step A: Preparation of Methyl 4-Amino-3-hydroxybenzoate

Through a solution of 4-amino-3-hydroxybenzoic acid (75 g, 0.49 mol) in 2.0 L of dry methanol at room temperature was bubbled anhydrous HCl gas until the solution was saturated. The solution was stirred for 48 hours, then concentrated in vacuo. The product was partitioned between EtOAc and saturated aq. $NaHCO_3$ solution, and the organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to provide the titled compound (79 g, 96% yield).

Step B: Preparation of Methyl 3-Hydroxy-4-iodobenzoate

A cloudy, dark solution of the product from Step A (79 g, 0.47 mol), 3N HCl (750 mL), and THF (250 mL) was cooled to 0°C. A solution of $NaNO_2$ (35.9 g, 0.52 mol) in 115 mL of water was added over ca. 5 minutes, and the solution was stirred for another 25 minutes. A solution of potassium iodide (312 g, 1.88 mol) in 235 mL of water was added all at once, and the reaction was stirred for an additional 15 minutes. The mixture was poured into EtOAc, shaken, and the layers were separated. The organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo to provide the crude product (148 g). Purification by column chromatography through silica gel (0%-50% EtOAc/hexane) provided the titled product (96 g, 73% yield).

Step C: Preparation of Methyl 4-Cyano-3-hydroxybenzoate

A mixture of the iodide product from Step B (101 g, 0.36 mol) and zinc(II)cyanide (30 g, 0.25 mol) in 400 mL of dry DMF was degassed by bubbling argon through the solution for 20 minutes. Tetrakis(triphenylphosphine)palladium (8.5 g, 7.2 mmol) was added, and the solution was heated to 80°C for 4 hours. The

solution was cooled to room temperature, then stirred for an additional 36 hours. The reaction was poured into EtOAc/water, and the organic layer was washed with brine (4x), dried (Na_2SO_4), and concentrated in vacuo to provide the crude product. Purification by column chromatography through silica gel (30%-50% EtOAc/hexane) provided the titled product (48.8 g, 76% yield).

Step D: Preparation of Methyl 4-Cyano-3-methoxybenzoate

Sodium hydride (9 g, 0.24 mol as 60% wt. disp. mineral oil) was aded to a solution of the phenol from Step C (36.1 g, 204 mmol) in 400 mL of dry DMF at room temperature. Iodomethane was added (14 mL. 0.22 mol) was added, and the reaction was stirred for 2 hours. The mixture was poured into EtOAc/water, and the organic layer was washed with water and brine (4x), dried (Na_2SO_4), and concentrated in vacuo to provide the titled product (37.6 g, 96% yield).

Step E: Preparation of 4-Cyano-3-methoxybenzyl Alcohol

To a solution of the ester from Step D (48.8 g, 255 mmol) in 400 mL of dry THF under argon at room temperature was added lithium borohydride (255 mL, 510 mmol, 2M THF) over 5 minutes. After 1.5 hours, the reaction was warmed to reflux for 0.5 hours, then cooled to room temperature. The solution was poured into EtOAc/1N HCl soln. [CAUTION], and the layers were separated. The organic layer was washed with water, sat Na_2CO_3 soln. and brine (4x), dried (Na_2SO_4), and concentrated in vacuo to provide the titled product (36.3 g, 87% yield).

Step F: Preparation of 4-Cyano-3-methoxybenzyl Bromide

A solution of the alcohol from Step E (35.5 g, 218 mmol) in 500 mL of dry THF was cooled to 0°C. Triphenylphosphine was added (85.7 g, 327 mmol), followed by carbontetrabromide (108.5 g, 327 mmol). The reaction was stirred at 0°C for 30 minutes, then at room temperature for 21 hours.

Silica gel was added (ca. 300 g), and the suspension was concentrated in vacuo. The resulting solid was loaded onto a silica gel chromatography column. Purification by flash chromatography (30%-50% EtOAc/hexane) provided the titled product (42 g, 85% yield).

Step G: Preparation of 1-(4-cyano-3-methoxybenzyl)-5-(acetoxymethyl)-imidazole hydrobromide

The titled product was prepared by reacting the bromide from Step F (21.7 g, 96 mmol) with the imidazole product from Step B of Example 1 (34.9 g, 91 mmol) using the procedure outlined in Step C of Example 1. The crude product was triturated with hexane to provide the titled product hydrobromide (19.43 g, 88% yield).

Step H: Preparation of 1-(4-cyano-3-methoxybenzyl)-5-(hydroxymethyl)-imidazole

The titled product was prepared by hydrolysis of the acetate from Step G (19.43 g, 68.1 mmol) using the procedure outlined in Step D of Example 1. The crude titled product was isolated in modest yield (11 g, 66% yield). Concentration of the aqueous extracts provided solid material (ca. 100 g) which contained a significant quantity of the titled product , as judged by ^{1}H NMR spectroscopy.

Step I: Preparation of 1-(4-cyano-3-methoxybenzyl)-5-imidazolecarboxaldehyde

The titled product was prepared by oxidizing the alcohol from Step H (11 g, 45 mmol) using the procedure outlined in Step E of Example 1. The titled aldehyde was isolated as a white powder (7.4 g, 68% yield) which was sufficiently pure for use in the next step without further purification.

Step J: Preparation of 1-(3-chlorophenyl)-4-[1-(4-cyano-3-methoxybenzyl)imidazolylmethyl]-2-piperazinone dihydrochloride

The titled product was prepared by reductive alkylation of the aldehyde from Step I (859 mg, 3.56 mmol) and the amine (hydrochloride) from Step K of Example 1 (800 mg, 3.24 mmol) using the procedure outlined in Step H of Example 1. Purification by flash column chromatography through silica gel (50%-75% acetone CH_2Cl_2) and conversion of the resulting white foam to its dihydrochloride salt provided the titled product as a white powder (743 mg, 45% yield). FAB ms (m+1) 437.

Anal. Calc. for $C_{23}H_{23}ClN_5O_2$•2.0HCl•0.35CH_2Cl_2:

C, 51.97; H, 4.80; N, 12.98.

Found: C, 52.11; H, 4.80; N, 12.21.

EXAMPLE 7

1-(3-trifluoromethoxyphenyl)-4-[1-(4-cyano-3-methoxybenzyl)imidazolyl methyl]-2-piperazinone dihydrochloride

1-(3-trifluoromethoxy-phenyl)-2-piperazinone hydrochloride was prepared from 3-trifluoromethoxyaniline using Steps F-J of Example 1. This amine (1.75 g, 5.93 mmol) was coupled to the aldehyde from Step I of Example 6 (1.57 g, 6.52 mmol) using the procedure outlined in Step H of Example 1. Purification by flash column chromatography through silica gel (60%-100% acetone CH_2Cl_2) and conversion of the resulting white foam to its dihydrochloride salt provided the titled product as a white powder (1.947 g, 59% yield). FAB ms (m+1) 486.

Anal. Calc. for $C_{24}H_{23}F_3N_5O_3$•2.0HCl•0.60H_2O:

C, 50.64; H, 4.46; N, 12.30.

Found: C, 50.69; H, 4.52; N, 12.13.

EXAMPLE 8

4-[((1-(4-cyanobenzyl)-5-imidazolyl)methyl)amino]benzophenone hydrochloride

The titled product was prepared by reductive alkylation of the aldehyde from Step E of Example 1 (124 mg, 0.588 mmol) and 4-aminobenzophenone (116 mg, 0.588 mmol) using the procedure outlined in Step K of Example 1. Purification by flash column chromatography through silica gel (2-6% MeOH/CH_2Cl_2) and conversion to the hydrochloride salt provided the titled product as a white solid (126 mg, 50% yield). FAB ms (m+1) 393.11.

Anal. Calc. for $C_{25}H_{20}N_5O \bullet 1.40HCl \bullet 0.40H_2O$:

C, 66.62; H, 4.96; N, 12.43.

Found: C, 66.73; H, 4.94; N, 12.46.

EXAMPLE 9

N-{1-(4-Cyanobenzyl)-1H-imidazol-5-ylethyl}-4(R)-benzyloxy-2(S)-{N'-acetyl-N'-3-chlorobenzyl}aminomethylpyrolidine

Step A: 4(R)-Hydroxyproline methyl ester

A suspension of 4(R)-hydroxyproline (35.12g, 267.8 mmol) in methanol (500ml) was saturated with gaseous hydrochloric acid. The resulting solution was allowed to stand for 16hrs and the solvent evaporated in vacuo to afford the title compound as a white solid.

^{1}H NMR CD_3OD δ 4.60 (2H, m), 3.86(3H, s), 3.48(1H, dd, J=3.6 and 12.0Hz), 3.23(1H, d, J=12.0Hz), 2.43(1H, m) and 2.21(1H, m) ppm.

Step B: N-t-Butoxycarbonyl-4(R)-hydroxyproline methyl ester

To a solution of 4(R)-hydroxyproline methyl ester (53.5g, 268mmol), and triethylamine (75ml, 540mmol), in CH_2Cl_2 (500ml), at 0°C, was added a solution of di-t-butyl dicarbonate

(58.48, 268mmol), in CH_2Cl_2 (75ml). The resulting mixture was stirred for 48hrs at room temperature. The solution was washed with 10% aqueous citric acid solution, saturated $NaHCO_3$ solution, dried (Na_2SO_4) and the solvent evaporated in vacuo. The title compound was obtained as a yellow oil and used in the next step without furthur purification.

^{1}H NMR CD_3OD δ 4.40-4.30 (2H, m), 3.75(3H, m), 3.60-3.40(2H, m), 2.30(1H, m), 2.05(1H, m) and 1.55-1.40(9H, m) ppm.

Step C: N-t-Butoxycarbonyl-4(R)-t-butyldimethylsilyloxy proline methyl ester

To a solution of N-t-butoxycarbonyl-4(R)-hydroxy proline methyl ester (65.87g, 268mmol), and triethylamine (41ml, 294mmol), in CH_2Cl_2 (536ml), at 0°C, was added a solution of t-butyldimethyl silylchloide (42.49g, 282mmol), in CH_2Cl_2 (86ml). The resulting mixture was stirred for 16hrs at room temperature. The solution was washed with 10% aqueous citric acid solution, saturated $NaHCO_3$ solution, dried (Na_2SO_4) and the solvent evaporated in vacuo. The title compound was obtained as a yellow oil and used in the next step without furthur purification.

^{1}H NMR CD_3OD δ 4.60-4.40 (2H, m), 3.75(3H, m), 3.60-3.20(2H, m), 2.30-1.90(2H, m), 1.45-1.40(9H, m), 0.90-0.85(9H, m), 0.10-0.00(6H, m) ppm.

Step D: N-t-Butoxycarbonyl-4(R)-t-butyldimethylsilyloxy-2(S)-hydroxymethylpyrrolidine

A solution of N-t-butoxycarbonyl-4-(R)-t-butyldimethyl-silyloxy proline methyl ester (86.65g, 241mmol), in THF (150ml), was added over 90 minutes to a solution of lithium aluminum hydride (247ml of a 1M solution in THF, 247mmol), under argon, so that the temperature did not exceed 12°C. Stirring was continued for 50 mins and then EtOAc (500ml) was added cautiously, followed by sodium sulphate decahydrate (34g), and the resulting mixture stirred for 16 hrs at room temperature. Anhydrous Na_2SO_4 (34g) was added and

the mixture stirred an additional 30 min and then filtered. The solids were washed with EtOAc (800ml), the filtrates combined and the solvent evaporated in vacuo. The title compound was obtained as a colourless oil and used in the next step without further purification.

Step E: N-t-Butoxycarbonyl-4(R)-t-butyldimethylsilyloxy-2(S)-methanesulfonyloxymethylpyrrolidine

To a solution of N-t-butoxycarbonyl-4(R)-t-butyldimethylsilyloxy-2(S)-hydroxymethylpyrrolidine (50.0g, 150.8mmol) and triethylamine (42.0ml, 300 mmol) in CH_2Cl_2(1 l) was added methane sulfonyl chloride (12.4ml, 160mmol) over a period of 5 minutes and stirring was continued for 1 hour. The solvent was evaporated in vacuo diluted with EtOAc (800mL) and washed sequentially with aqueous citric acid and $NaHCO_3$. The organic extracts were dried (Na2SO4), evaporated in vacuo and the residue purified by chromatography (SiO2, 15% EtOAc in hexanes). The title compound was obtained as a pale yellow solid

FAB Mass spectrum, m/z = 410(M+1).

^{1}H NMR CDCl3 δ 4.60-4.00 (4H, m), 3.60-3.30(2H, m), 2.98(3H, s), 2.05-2.00(2H, m), 1.48-1.42(9H, m),0.90-0.80(9H, m), 0.10-0.00(6H, m) ppm.

Step F: Preparation of N-t-Butoxycarbonyl-4(R)-t-butyldimethylsilyloxy-2(S)-azidomethylpyrrolidine

In a flask protected by a safety screen, a solution of N-t-butoxycarbonyl-4(S)-t-butyldimethylsilyloxy-2(S)-methane-sulfonyloxy methyl pyrrolidine(10.40g, 25.39mmol) and tetrabutyl-ammonium azide (8.18g, 28.7mmol) in toluene (250ml) was stirred at 80°C for 5hr. The reaction was cooled to room temperature and diluted with EtOAc (250ml), washed with water and brine and dried (Na_2SO_4). The solvent was evaporated in vacuo to afford the title compound as a yellow oil which was used in the next step without furthur purification.

^{1}H NMR CDCl3 δ 4.60-3.20 (6H, m), 2.05-1.90(2H, m),

1.47(9H, s), 0.87(9H, s) and 0.10-0.00(6H, m) ppm.

Step G: Preparation of N-t-Butoxycarbonyl-4(R)-t-butyldimethylsilyloxy-2(S)-aminomethylpyrrolidine

A solution of N-t-butoxycarbonyl-4(R)-t-butyldimethylsilyloxy-2(S)-azidomethylpyrrolidine (9.06g, 25.39mmol) in EtOAc (120ml) was purged with argon and 10% palladium on carbon (1.05g) added. The flask was evacuated and stirred under an atmosphere of hydrogen (49 psi) for 16hrs. The hydrogen was replaced by argon, the catalyst removed by filtration and the solvent evaporated in vacuo. The residue was chromatographed (SiO_2, 2.5 to 5% saturated NH_4OH in acetonitrile, gradient elution), to afford the title compound as an oil.

^1H NMR($CDCl_3$, 400 MHz) δ 4.40-2.60 (6H, s), 2.05-1.80(2H, m), 1.46(9H, s), 1.36(2H, s), 0.87(9H, s), 0.10-0.00(6H, m)ppm.

Step H: Preparation of N-t-Butoxycarbonyl-4(R)-t-butyldimethylsilyloxy-2(S)-{N'-3-chlorobenzyl}aminomethylpyrrolidine

To a slurry of 3-chlorobenzaldehyde (1.2ml, 10.6mmol), crushed 3A molecular sieves (9.5g) and the amine from step G (3.50g, 10.6mmol) in methanol (150 ml) was added sodium cyanoborohydride (11.0ml of a 1M solution in THF, 11.0mmol) at room temperature. The pH was adjusted to 7 by the addition of glacial acetic acid (0.68ml, 12mmol) and the reaction was stirred for 16 hrs. The reaction was filtered and the filtrate evaporated in vacuo. The residue was partitioned between EtOAc and saturated $NaHCO_3$ solution and the organic extract washed with brine, dried (Na_2SO_4), and the solvent evaporated in vacuo. The residue was purified by chromatography (SiO_2, 2.5% MeOH in CH_2Cl_2) to provide the title compound as an oil.

^1HNMR($CDCl_3$, 400 MHz) δ 7.40-7.10(4H, m), 4.36(1H, s), 4.15-3.90(2H, m), 3.90-3.30(2H, m), 2.85-2.60(2H, m), 2.05-1.90(2H, m), 1.44(9H, s), 0.87(9H, s) and 0.06(6H, m) ppm.

<u>Step I:</u> <u>Preparation of N-t-Butoxycarbonyl-4(R)-t-butyldimethylsilyloxy-2(S)-{N'-3-chlorobenzyl-N'-acetyl}- aminomethylpyrrolidine</u>

To a solution of N-t-butoxycarbonyl-4(R)-t-butyldimethylsilyloxy-2(S)-{N'-3-chlorobenzyl}-aminomethyl pyrrolidine (3.80g, 8.35 mmol) in CH_2Cl_2 (85ml) and triethylamine (2.40ml, 17.0 mmol) at 0°C was added acetyl chloride (0.60ml, 8.44 mmol). The reaction was stirred at room temperature for 1hr, diluted with water and extracted with CH_2Cl_2. The extracts were washed with brine, dried (Na_2SO_4) and the solvent evaporated in vacuo. The residue was purified by chromatography (SiO_2, 10 to 25% EtOAc in CH_2Cl_2, gradient elution).

^{1}HNMR ($CDCl_3$, 400 MHz) δ 7.40-7.00(4H, m), 5.10-3,00(8H, m), 2.20-1.70(5H, m), 1.50-1.30(9H, m), 0.87(9H, s) and 0.06(6H, m) ppm.

<u>Step J:</u> <u>Preparation of N-t-Butoxycarbonyl-4(R)-hydroxy-2(S)-{N' -3-chlorobenzyl-N'-acetyl}-aminomethylpyrrolidine</u>

To a solution of N-t-butoxycarbonyl-4(R)-t-butyldimethylsilyloxy -2(S)-{N'-3-chlorobenzyl-N'-acetyl}-aminomethylpyrrolidine (4.02g, 8.09 mmol) in THF (80ml) at 0°C was added tetrabutylammonium fluoride (9.00ml of a 1M solution in THF, 9.00mmol). The reaction was stirred at 0°C for 1hr and then at room temperature for 30min. The reaction was quenched by the addition of a saturated NH_4Cl solution (50ml), dilution with EtOAc. The organic extracts were washed with brine, dried (Na_2SO_4) and the solvent evaporated in vacuo. The residue purified by chromatography (SiO_2, 3 to 5% MeOH in CH_2Cl_2, gradient elution) to afford the title compound as a foam.

^{1}HNMR ($CDCl_3$, 400 MHz) δ 7.40-7.00(4H, m), 5.00-4,00(4H, m), 4.00-3.10(4H, m), 2.30-1.60(5H, m) and 1.50-1.30(9H, m) ppm.

<u>Step K:</u> <u>N-t-Butoxycarbonyl-4(R)-benzyloxyoxy-2(S)-{N'-acetyl-N'-3-chlorobenzyl}aminomethylpyrrolidine</u>

To a solution of N-t-Butoxycarbonyl-4(S)-hydroxy-2(S)-{N'-acetyl-N' 3-chlorobenzyl}aminomethylpyrrolidine (701mg, 1.83 mmol) in DMF (9ml) at 0°C was added sodium hydride (110mg of a 60% dispersion in mineral oil, 2.75mmol). After 15 min benzyl bromide (0.435ml, 3.66mmol), was added and the reaction stirred at room temperature for 16 hrs. The reaction was quenched with saturated $NaHCO_3$ solution (2ml) and extracted with ethyl acetate.. The organic extract was washed with brine and dried (Na_2SO_4), and the solvent evaporated in vacuo. The residue was purified by chromatography (SiO_2, 25 to 50% EtOAc in CH_2Cl_2, gradient elution) to afford the title compound as a foam.

Step L: 4(S)-Benzyloxy-2(S)-{N'-acetyl-N'-3-chlorobenzyl}-aminomethylpyrrolidine hydrochloride

A solution of the product from step K (0.834g, 1.76 mmol) in EtOAc (25 ml) at 0°C was saturated with gaseous hydrogen chloride. The resulting solution was allowed to stand at room temperature for 30min. The solvent was evaporated in vacuo to afford the title compound as a white solid.

Step M: Preparation of 1H-Imidazole-4- acetic acid methyl ester hydrochloride.

A solution of 1H-imidazole-4-acetic acid hydrochloride (4.00g, 24.6 mmol) in methanol (100 ml) was saturated with gaseous hydrogen chloride. The resulting solution was allowed to stand at room temperature (RT) for 18hr. The solvent was evaporated in vacuo to afford the title compound as a white solid.
^1H NMR($CDCl_3$, 400 MHz) δ 8.85(1H, s),7.45(1H, s), 3.89(2H, s) and 3.75(3H, s) ppm.

Step N: Preparation of 1-(Triphenylmethyl)-1H-imidazol-4-ylacetic acid methyl ester.

To a solution of the product from Step M (24.85g, 0.141mol) in dimethyl formamide (DMF) (115ml) was added triethylamine (57.2 ml, 0.412mol) and triphenylmethyl bromide

(55.3g, 0.171mol) and the suspension was stirred for 24hr. After this time, the reaction mixture was diluted with ethyl acetate (EtOAc) (1 l) and water (350 ml). The organic phase was washed with sat. aq. $NaHCO_3$ (350 ml), dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography (SiO_2, 0-100% ethyl acetate in hexanes; gradient elution) to provide the title compound as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35(1H, s), 7.31(9H, m), 7.22(6H, m), 6.76(1H, s), 3.68(3H, s) and 3.60(2H, s) ppm.

Step O: Preparation of [1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetic acid methyl ester.

To a solution of the product from Step N (8.00g, 20.9mmol) in acetonitrile (70 ml) was added bromo-p-tolunitrile (4.10g, 20.92 mmol) and heated at 55°C for 3 hr. After this time, the reaction was cooled to room temperature and the resulting imidazolium salt (white precipitate) was collected by filtration. The filtrate was heated at 55°C for 18hr. The reaction mixture was cooled to room temperature and evaporated in vacuo. To the residue was added EtOAc (70 ml) and the resulting white precipitate collected by filtration. The precipitated imidazolium salts were combined, suspended in methanol (100 ml) and heated to reflux for 30min. After this time, the solvent was removed in vacuo, the resulting residue was suspended in EtOAc (75ml) and the solid isolated by filtration and washed (EtOAc). The solid was treated with sat aq $NaHCO_3$ (300ml) and CH_2Cl_2 (300ml) and stirred at room temperature for 2 hr. The organic layer was separated, dried ($MgSO_4$) and evaporated in vacuo to afford the title compound as a white solid :

^{1}HNMR($CDCl_3$, 400 MHz) δ 7.65(1H, d, J=8Hz), 7.53(1H, s), 7.15(1H, d, J=8Hz), 7.04(1H, s), 5.24(2H, s), 3.62(3H, s) and 3.45(2H, s) ppm.

Step P: Preparation of (1-(4-Cyanobenzyl)-1H-imidazol-5-yl)-ethanol

To a stirred solution of the ester from step O, (1.50g, 5.88mmol), in methanol (20ml) at 0°C, was added sodium borohydride (1.0g, 26.3mmol) portionwise over 5 minutes. The reaction was stirred at 0°C for 1 hr and then at room temperature for an additional 1 hr. The reaction was quenched by the addition of sat.NH_4Cl solution and the methanol was evaporated *in vacuo*.. The residue was partitioned between EtOAc and sat $NaHCO_3$ solution and the organic extracts dried ($MgSO_4$), and evaporated *in vacuo*.. The residue was purified by chromatography (SiO_2, 4 to 10% methanol in methylene chloride, gradient elution) to afford the title compound as a solid.

^{1}H NMR $CDCl_3$ δ 7.64(2H, d, J=8.2Hz), 7.57(1H, s), 7.11(2H, d, J=8.2Hz), 6.97(1H, s), 5.23(2H, s), 3.79(2H, t, J=6.2Hz) and 2.66(2H, t, J=6.2Hz) ppm.

Step Q: 1-(4-Cyanobenzyl)-imidazol-5-yl-ethylmethanesulfonate

A solution of (1-(4-Cyanobenzyl)-1H-imidazol-5-yl)-ethanol (0.500 g, 2.20 mmol) in methylene chloride (6.0 ml) at 0°C was treated with Hunig's base (0.460ml, 2.64mmol) and methane sulfonyl chloride (0.204ml, 2.64mmol). After 2 hrs, the reaction was quenched by addition of saturated $NaHCO_3$ solution (50ml) and the mixture was extracted with methylene chloride (50ml), dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The title compound was used without furthur purification.

^{1}H NMR $CDCl_3$ δ 7.69 (1H, s) 7.66(2H, d, J=8.2Hz), 7.15 (2H, d, J=8.2Hz), 7.04(1H, s), 5.24(2H, s), 4.31(2H, t, J=6.7Hz), 2.96(3H, s), and 2.88(2H, t, J=6.6Hz)ppm.

Step R: N{1-(4-Cyanobenzyl)-1H--imidazol-5-ylethyl}-4(R)-benzyloxyoxy-2(S)-{N'-acetyl-N'-3-chlorobenzyl}aminomethylpyrrolidine

A mixture of 4(R)-benzyloxy-2(S)-{N'-acetyl-N'-3-chlorobenzyl-aminomethyl}pyrrolidine (199mg, 0.486mmol), the mesylate from step Q (140mg, 0.458mmol), potassium carbonate

(165mg, 1.19mmol), and sodium iodide (289mg, 1.93mmol) in DMF (1.5ml), were heated at 55°C for 16 hrs. The cooled mixture was diluted with EtOAc, washed with $NaHCO_3$ solution and brine , dried (Na_2SO_4) and the solvent evaporated in vacuo. The residue was purified by preparative HPLC (C-18, 95:5 to 5:95 water in acetonitrile containing 0.1% TFA, gradient elution). The title compound was obtained as a white solid after lyophillisation.

Anal. calc'd for $C_{34}H_{36}N_5O_2Cl$ 3.00 TFA, 0.85 H_2O:

C, 51.14; H, 4.37, N, 7.45.

Found: C, 51.15; H, 4.42; N, 6.86.

FAB HRMS exact mass calc'd for $C_{34}H_{37}N_5O_2Cl$

582.263579(MH+),

Found: 582.263900.

EXAMPLE 10

In vitro inhibition

Transferase Assays. Isoprenyl-protein transferase activity assays are carried out at 30 °C unless noted otherwise. A typical reaction contains (in a final volume of 50 μL): [^{3}H]farnesyl diphosphate or [^{3}H]geranylgeranyl diphosphate, Ras protein , 50 mM HEPES, pH 7.5, 5 mM $MgCl_2$, 5 mM dithiothreitol, 10 μM $ZnCl_2$, 0.1% polyethyleneglycol (PEG) (15,000-20,000 mw) and isoprenyl-protein transferase. The FPTase employed in the assay is prepared by recombinant expression as described in Omer, C.A., Kral, A.M., Diehl, R.E., Prendergast, G.C., Powers, S., Allen, C.M., Gibbs, J.B. and Kohl, N.E. (1993) *Biochemistry* 32:5167-5176. The geranylgeranyl-protein transferase-type I employed in the assay is prepared as described in U.S. Pat. No. 5,470,832, incorporated by reference. After thermally pre-equilibrating the assay mixture in the absence of enzyme, reactions are initiated by the addition of isoprenyl-protein transferase and stopped at timed intervals (typically 15 min) by the addition of 1 M HCl in ethanol (1 mL). The quenched reactions are allowed to stand for 15 m (to complete the precipitation process). After adding 2 mL of 100% ethanol, the reactions are vacuum-filtered through Whatman GF/C

filters. Filters are washed four times with 2 mL aliquots of 100% ethanol, mixed with scintillation fluid (10 mL) and then counted in a Beckman LS3801 scintillation counter.

For inhibition studies, assays are run as described above, except inhibitors are prepared as concentrated solutions in 100% dimethyl sulfoxide and then diluted 20-fold into the enzyme assay mixture. Substrate concentrations for inhibitor IC_{50} determinations are as follows: FTase, 650 nM Ras-CVLS (SEQ.ID.NO.: 11), 100 nM farnesyl diphosphate; GGPTase-I, 500 nM Ras-CAIL (SEQ.ID.NO.: 12), 100 nM geranylgeranyl diphosphate.

EXAMPLE 11

Modified*In vitro* GGTase inhibition assay

The modified geranylgeranyl-protein transferase inhibition assay is carried out at room temperature. A typical reaction contains (in a final volume of 50 µL): [^{3}H]geranylgeranyl diphosphate, biotinylated Ras peptide, 50 mM HEPES, pH 7.5, a modulating anion (for example 10 mM glycerophosphate or 5mM ATP), 5 mM $MgCl_2$, 10 µM $ZnCl_2$, 0.1% PEG (15,000-20,000 mw), 2 mM dithiothreitol, and geranylgeranyl-protein transferase type I(GGTase). The GGTase-type I enzyme employed in the assay is prepared as described in U.S. Pat. No. 5,470,832, incorporated by reference. The Ras peptide is derived from the K4B-Ras protein and has the following sequence: biotinyl-GKKKKKKSKTKCVIM (single amino acid code) (SEQ.ID.NO.: 14). Reactions are initiated by the addition of GGTase and stopped at timed intervals (typically 15 min) by the addition of 200 µL of a 3 mg/mL suspension of streptavidin SPA beads (Scintillation Proximity Assay beads, Amersham) in 0.2 M sodium phosphate, pH 4, containing 50 mM EDTA, and 0.5% BSA. The quenched reactions are allowed to stand for 2 hours before analysis on a Packard TopCount scintillation counter.

For inhibition studies, assays are run as described above, except inhibitors are prepared as concentrated solutions in 100% dimethyl sulfoxide and then diluted 25-fold into the enzyme assay

mixture. IC_{50} values are determined with Ras peptide near K_M concentrations. Enzyme and substrate concentrations for inhibitor IC_{50} determinations are as follows: 75 pM GGTase-I, 1.6 μM Ras peptide, 100 nM geranylgeranyl diphosphate.

EXAMPLE 12

The processing assays employed are modifications of that described by DeClue et al [Cancer Research 51, 712-717, 1991].

K4B-Ras processing inhibition assay

PSN-1 (human pancreatic carcinoma) or viral-K4B-*ras*-transformed Rat1 cells are used for analysis of protein processing. Subconfluent cells in 100 mm dishes are fed with 3.5 ml of media (methionine-free RPMI supplemented with 2% fetal bovine serum or cysteine-free/methionine-free DMEM supplemented with 0.035 ml of 200 mM glutamine (Gibco), 2% fetal bovine serum, respectively) containing the desired concentration of test compound, lovastatin or solvent alone. Cells treated with lovastatin (5-10 μM), a compound that blocks Ras processing in cells by inhibiting a rate-limiting step in the isoprenoid biosynthetic pathway, serve as a positive control. Test compounds are prepared as 1000x concentrated solutions in DMSO to yield a final solvent concentration of 0.1%. Following incubation at 37°C for two hours 204 μCi/ml [^{35}S]Pro-Mix (Amersham, cell labeling grade) is added.

After introducing the label amino acid mixture, the cells are incubated at 37°C for an additional period of time (typically 6 to 24 hours). The media is then removed and the cells are washed once with cold PBS. The cells are scraped into 1 ml of cold PBS, collected by centrifugation (10,000 x g for 10 sec at room temperature), and lysed by vortexing in 1 ml of lysis buffer (1% Nonidet P-40, 20 mM HEPES, pH 7.5, 150 mM NaCl, 1 mM EDTA, 0.5% deoxycholate, 0.1% SDS, 1 mM DTT, 10 μg/ml AEBSF, 10 μg/ml aprotinin, 2 μg/ml leupeptin and 2 μg/ml antipain). The lysate is then centrifuged at 15,000 x g for 10 min at 4°C and the supernatant saved.

For immunoprecipitation of Ki4B-Ras, samples of lysate supernatant containing equal amounts of protein are utilized. Protein concentration is determined by the bradford method utilizing bovine serum albumin as a standard. The appropriate volume of lysate is brought to 1 ml with lysis buffer lacking DTT and 8 μg of the pan Ras monoclonal antibody, Y13-259, added. The protein/antibody mixture is incubated on ice at 4°C for 24 hours. The immune complex is collected on pansorbin (Calbiochem) coated with rabbit antiserum to rat IgG (Cappel) by tumbling at 4°C for 45 minutes. The pellet is washed 3 times with 1 ml of lysis buffer lacking DTT and protease inhibitors and resuspended in 100 μl elution buffer (10 mM Tris pH 7.4, 1% SDS). The Ras is eluted from the beads by heating at 95°C for 5 minutes, after which the beads are pelleted by brief centrifugation (15,000 x g for 30 sec. at room temperature).

The supernatant is added to 1 ml of Dilution Buffer 0.1% Triton X-100, 5 mM EDTA, 50 mM NaCl, 10 mM Tris pH 7.4) with 2 μg Kirsten-ras specific monoclonal antibody, c-K-ras Ab-1 (Calbiochem). The second protein/antibody mixture is incubated on ice at 4°C for 1-2 hours. The immune complex is collected on pansorbin (Calbiochem) coated with rabbit antiserum to rat IgG (Cappel) by tumbling at 4°C for 45 minutes. The pellet is washed 3 times with 1 ml of lysis buffer lacking DTT and protease inhibitors and resuspended in Laemmli sample buffer. The Ras is eluted from the beads by heating at 95°C for 5 minutes, after which the beads are pelleted by brief centrifugation. The supernatant is subjected to SDS-PAGE on a 12% acrylamide gel (bis-acrylamide:acrylamide, 1:100), and the Ras visualized by fluorography.

EXAMPLE 13

Rap1 processing inhibition assay

Protocol A:

Cells are labeled, incubated and lysed as described in Example 12.

For immunoprecipitation of Rap1, samples of lysate supernatant containing equal amounts of protein are utilized. Protein concentration is determined by the bradford method utilizing bovine serum albumin as a standard. The appropriate volume of lysate is brought to 1 ml with lysis buffer lacking DTT and 2 μg of the Rap1 antibody, Rap1/Krev1 (121) (Santa Cruz Biotech SC/65), is added. The protein/antibody mixture is incubated on ice at 4°C for 1 hour. The immune complex is collected on pansorbin (Calbiochem) by tumbling at 4°C for 45 minutes. The pellet is washed 3 times with 1 ml of lysis buffer lacking DTT and protease inhibitors and resuspended in 100 μl elution buffer (10 mM Tris pH 7.4, 1% SDS). The Rap1 is eluted from the beads by heating at 95°C for 5 minutes, after which the beads are pelleted by brief centrifugation (15,000 x g for 30 sec. at room temperature).

The supernatant is added to 1 ml of Dilution Buffer (0.1% Triton X-100, 5 mM EDTA, 50 mM NaCl, 10 mM Tris pH 7.4) with 2 μg Rap1 antibody, Rap1/Krev1 (121) (Santa Cruz Biotech). The second protein/antibody mixture is incubated on ice at 4°C for 1-2 hours. The immune complex is collected on pansorbin (Calbiochem) by tumbling at 4°C for 45 minutes. The pellet is washed 3 times with 1 ml of lysis buffer lacking DTT and protease inhibitors and resuspended in Laemmli sample buffer. The Rap1 is eluted from the beads by heating at 95°C for 5 minutes, after which the beads are pelleted by brief centrifugation. The supernatant is subjected to SDS-PAGE on a 12% acrylamide gel (bis-acrylamide:acrylamide, 1:100), and the Rap1 visualized by fluorography.

Protocol B:

PSN-1 cells are passaged every 3-4 days in 10cm plates, splitting near-confluent plates 1:20 and 1:40. The day before the assay is set up, 5x 10^6 cells are plated on 15cm plates to ensure the same stage of confluency in each assay. The media for these cells is RPM1 1640 (Gibco), with 15% fetal bovine serum and 1x Pen/Strep antibiotic mix.

The day of the assay, cells are collected from the 15cm plates by trypsinization and diluted to 400,000 cells/ml in media. 0.5ml of these diluted cells are added to each well of 24-well plates, for a final cell number of 200,000 per well. The cells are then grown at 37°C overnight.

The compounds to be assayed are diluted in DMSO in 1/2-log dilutions. The range of final concentrations to be assayed is generally 0.1-100µM. Four concentrations per compound is typical. The compounds are diluted so that each concentration is 1000x of the final concentration (i.e., for a 10µM data point, a 10mM stock of the compound is needed).

2µL of each 1000x compound stock is diluted into 1ml media to produce a 2X stock of compound. A vehicle control solution (2µL DMSO to 1ml media), is utilized. 0.5 ml of the 2X stocks of compound are added to the cells.

After 24 hours, the media is aspirated from the assay plates. Each well is rinsed with 1ml PBS, and the PBS is aspirated. 180µL SDS-PAGE sample buffer (Novex) containing 5% 2-mercaptoethanol is added to each well. The plates are heated to 100°C for 5 minutes using a heat block containing an adapter for assay plates. The plates are placed on ice. After 10 minutes, 20µL of an RNAse/DNase mix is added per well. This mix is 1mg/ml DNaseI (Worthington Enzymes), 0.25mg/ml Rnase A (Worthington Enzymes), 0.5M Tris-HCl pH8.0 and 50mM $MgCl_2$. The plate is left on ice for 10 minutes. Samples are then either loaded on the gel, or stored at -70°C until use.

Each assay plate (usually 3 compounds, each in 4-point titrations, plus controls) requires one 15-well 14% Novex gel. 25µl of each sample is loaded onto the gel. The gel is run at 15mA for about 3.5 hours. It is important to run the gel far enough so that there will be adequate separation between 21kd (Rap1) and 29kd (Rab6).

The gels are then transferred to Novex pre-cut PVDF membranes for 1.5 hours at 30V (constant voltage). Immediately after transferring, the membranes are blocked overnight in 20ml Western

blocking buffer (2% nonfat dry milk in Western wash buffer (PBS + 0.1% Tween-20). If blocked over the weekend, 0.02% sodium azide is added. The membranes are blocked at 4°C with slow rocking.

The blocking solution is discarded and 20ml fresh blocking solution containing the anti-Rap1A antibody (Santa Cruz Biochemical SC1482) at 1:1000 (diluted in Western blocking buffer) and the anti Rab6 antibody (Santa Cruz Biochemical SC310) at 1:5000 (diluted in Western blocking buffer) are added. The membranes are incubated at room temperature for 1 hour with mild rocking. The blocking solution is then discarded and the membrane is washed 3 times with Western wash buffer for 15 minutes per wash. 20ml blocking solution containing 1:1000 (diluted in Western blocking buffer) each of two alkaline phosphatase conjugated antibodies (Alkaline phosphatase conjugated Anti-goat IgG and Alkaline phosphatase conjugated anti-rabbit IgG [Santa Cruz Biochemical]) is then added. The membrane is incubated for one hour and washed 3x as above.

About 2ml per gel of the Amersham ECF detection reagent is placed on an overhead transparency (ECF) and the PVDF membranes are placed face-down onto the detection reagent. This is incubated for one minute, then the membrane is placed onto a fresh transparency sheet.

The developed transparency sheet is scanned on a phosphorimager and the Rap1A Minimum Inhibitory Concentration is determined from the lowest concentration of compound that produces a detectable Rap1A Western signal. The Rap1A antibody used recognizes only unprenylated/unprocessed Rap1a, so that the precence of a detectable Rap1A Western signal is indicative of inhibition of Rap1A prenylation.

The previously described Rap1/Krev1 (121) antibody may also be utilized in the Protocol B assay in place of the SC1482 antibody.

EXAMPLE 14

In vivo tumor growth inhibition assay (nude mouse)

In vivo efficacy as an inhibitor of the growth of cancer cells may be confirmed by several protocols well known in the art. Examples of such *in vivo* efficacy studies are described by N. E. Kohl et al. (*Nature Medicine*, 1:792-797 (1995)) and N. E. Kohl et al. (*Proc. Nat. Acad. Sci. U.S.A.*, 91:9141-9145 (1994)).

Rodent fibroblasts transformed with oncogenically mutated human H-*ras* or Ki-*ras* (10^6 cells/animal in 1 ml of DMEM salts) are injected subcutaneously into the left flank of 8-12 week old female nude mice (Harlan) on day 0. The mice in each oncogene group are randomly assigned to a vehicle, compound or combination treatment group. Animals are dosed subcutaneously starting on day 1 and daily for the duration of the experiment. Alternatively, the farnesyl-protein transferase inhibitor may be administered by a continuous infusion pump. Compound, compound combination or vehicle is delivered in a total volume of 0.1 ml. Tumors are excised and weighed when all of the vehicle-treated animals exhibited lesions of 0.5 - 1.0 cm in diameter, typically 11-15 days after the cells were injected. The average weight of the tumors in each treatment group for each cell line is calculated.

RELATED APPLICATION

The present patent application is a continuation-in-part application of copending provisional application Serial No. 60/057,228, filed August 27,1997.

WHAT IS CLAIMED IS:

1. A method of inhibiting prenyl-protein transferases which comprises administering to a mammal in need thereof a pharmaceutically effective amount of a compound, which is characterized by:

a) inhibition of greater than (>) 25% of the cellular processing of a newly synthesized protein that is a substrate of one or both of geranylgeranyl-protein transferase Type I and farnesyl-protein transferase after incubation of cells in the presence of the compound; and

b) an IC_{50} (a measurement of *in vitro* inhibitory activity) of less than about 1 μM against transfer of a farnesyl residue to a protein or peptide substrate comprising a $CAAX^F$ motif by farnesyl-protein transferase.

2. The method according to Claim 1 wherein the compound inhibits greater than 50% of the cellular processing of a newly synthesized protein that is a substrate of one or both of geranylgeranyl-protein transferase Type I and farnesyl-protein transferase.

3. The method according to Claim 1 which comprises administering to a mammal in need thereof a pharmaceutically effective amount of a compound, which is characterized by:

a) inhibition of greater than (>) 25% of the cellular processing of a newly synthesized protein that is a substrate of geranylgeranyl-protein transferase Type I or both of geranylgeranyl-protein transferase Type I and farnesyl-protein transferase after incubation of cells in the presence of the compound; and

b) an IC_{50} (a measurement of *in vitro* inhibitory activity) of less than about 1 μM against transfer of a farnesyl residue to a

protein or peptide substrate comprising a $CAAX^F$ motif by farnesyl-protein transferase.

4. The method according to Claim 1 wherein the newly synthesized protein in characteristic a) is a substrate of both geranylgeranyl-protein transferase Type I and farnesyl-protein transferase.

5. The method according to Claim 1 wherein the compound inhibits transfer of a farnesyl residue to a protein or peptide substrate comprising a $CAAX^F$ motif by farnesyl-protein transferase at an *in vitro* inhibitory activity (IC_{50}) of less than about 100 nM.

6. The method according to Claim 1 wherein the newly synthesized protein is selected from K4B-Ras and Rap1.

7. The method according to Claim 1 wherein the newly synthesized protein that is a substrate of geranylgeranyl-protein transferase Type I is K4B-Ras.

8. The method according to Claim 1 wherein the newly synthesized protein that is a substrate of geranylgeranyl-protein transferase Type I is Rap1.

9. The method according to Claim 1 wherein the cells are selected from PSN-1 cells and K-*ras*-transformed Rat1 cells.

10 A method of inhibiting farnesyl-protein transferase and geranylgeranyl-protein transferase type I which comprises administering to a mammal in need thereof a pharmaceutically effective amount of a compound, which is characterized by:

a) inhibition of greater than (>) 25% of the cellular processing of a newly synthesized protein that is a substrate of one or both of geranylgeranyl-protein transferase Type I and farnesyl-protein

transferase after incubation of cells in the presence of the compound;

b) an IC_{50} (a measurement of *in vitro* inhibitory activity) of less than about 1 μM against transfer of a farnesyl residue to a protein or peptide substrate comprising a $CAAX^F$ motif by farnesyl-protein transferase; and

c) an IC_{50} (a measurement of *in vitro* inhibitory activity) of less than about 5 μM against transfer of a geranylgeranyl residue to a protein or peptide substrate comprising a $CAAX^G$ motif by geranylgeranyl-protein transferase type I in the presence of a modulating anion.

11. The method according to Claim 10 wherein the compound inhibits greater than 50% of the cellular processing of a newly synthesized protein that is a substrate of one or both of geranylgeranyl-protein transferase Type I and farnesyl-protein transferase.

12. The method according to Claim 10 wherein the newly synthesized protein in characteristic a) is a substrate of both geranylgeranyl-protein transferase Type I and farnesyl-protein transferase.

13. The method according to Claim 10 wherein the compound inhibits transfer of a farnesyl residue to a protein or peptide substrate comprising a $CAAX^F$ motif by farnesyl-protein transferase at an IC_{50} of less than about 100 nM.

14. The method according to Claim 10 wherein the compound inhibits transfer of a geranylgeranyl residue to a protein or peptide substrate comprising a $CAAX^G$ motif by geranylgeranyl-protein transferase type I in the presence of a modulating anion at an IC_{50} of less than about 1 μM.

15. The method according to Claim 10 wherein the newly synthesized protein that is a substrate of geranylgeranyl-protein transferase Type I is selected from K4B-Ras and Rap1.

16. The method according to Claim 10 wherein the cells are selected from PSN-1 cells and K-*ras*-transformed Rat1 cells.

17. The method according to Claim 10 wherein the modulating anion is selected from: adenosine 5'-triphosphate, 2'-deoxyadenosine 5'-triphosphate, 2'-deoxycytosine 5'-triphosphate, β-glycerol phosphate, pyrophosphate, guanosine 5'-triphosphate, 2'-deoxyguanosine 5'-triphosphate, uridine 5'-triphosphate, dithiophosphate, thymidine 5'-triphosphate, tripolyphosphate, D-myo-inositol 1,4,5-triphosphate and sulfate.

18. The method according to Claim 17 wherein the modulating anion is selected from: adenosine 5'-triphosphate (ATP), β-glycerol phosphate, pyrophosphate, dithiophosphate and sulfate.

19. A method of treating cancer which comprises administering to a mammal in need thereof a pharmaceutically effective amount of a compound, which is characterized by:

a) inhibition of greater than (>) 25% of the cellular processing of a newly synthesized protein that is a substrate of one or both of geranylgeranyl-protein transferase Type I and farnesyl-protein transferase after incubation of cells in the presence of the compound.

20. The method according to Claim 19 wherein the compound inhibits greater than 50% of the cellular processing of a newly synthesized protein that is a substrate of one or both of geranylgeranyl-protein transferase Type I and farnesyl-protein transferase.

21. The method according to Claim 19 wherein the protein in characteristic a) is a substrate of both geranylgeranyl-protein transferase Type I and farnesyl-protein transferase.

22. The method according to Claim 19 wherein the newly synthesized protein is selected from K4B-Ras and Rap1.

23. The method according to Claim 19 wherein the newly synthesized protein that is a substrate of geranylgeranyl-protein transferase Type I is K4B-Ras.

24. The method according to Claim 19 wherein the newly synthesized protein that is a substrate of geranylgeranyl-protein transferase Type I is Rap-1.

25. The method according to Claim 19 wherein the cells are selected from PSN-1 cells and K-*ras*-transformed Rat1 cells.

26. The method according to Claim 19 wherein the compound is selected from:
1-[2(R)-Amino-3-mercaptopropyl]-2(S)-[(3-pyridyl)methoxyethyl)]-4-(1-naphthoyl)piperazine

1-[2(R)-Amino-3-mercaptopropyl]-2(S)-(benzyloxymethyl)-4-(1-naphthoyl)piperazine

1-[2(R)-Amino-3-mercaptopropyl]-2(S)-(benzyloxymethyl)-4-[7-(2,3-dihydrobenzofuroyl)]piperazine

1-[2(R)-Amino-3-mercaptopropyl]-2(S)-(benzamido)-4-(1-naphthoyl)piperazine

1-[2(R)-Amino-3-mercaptopropyl]-2(S)-[4-(5-dimethylamino-1-naphyhalenesulfonamido)-1-butyl]-4-(1-naphthoyl)piperazine

N-[2(S)-(1-(4-Nitrophenylmethyl)-1H-imidazol-5-ylacetyl)amino-3(S)-methylpentyl]-N-1-naphthylmethyl-glycyl-methionine

N-[2(S)-(1-(4-Nitrophenylmethyl)-1H-imidazol-5-ylacetyl)amino-3(S)-methylpentyl]-N-1-naphthylmethyl-glycyl-methionine methyl ester

N-[2(S)-([1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetylamino)-3(S)-methylpentyl]-N-(1-naphthylmethyl)glycyl-methionine

N-[2(S)-([1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetylamino)-3(S)-methylpentyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(2-naphthylmethyl)imidazol-5-ylmethyl]-piperazine

2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine

1-{[1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetyl}-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine

1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)imidazolylmethyl]-2-piperazinone

1-phenyl-4-[1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl]-piperazin-2-one

1-(3-trifluoromethylphenyl)-4-[1-(4-cyanobenzyl)-1H-imidazol-5-ylmethyl]-piperazin-2-one

1-(3-bromophenyl)-4-[1-(4-cyanobenzyl)-1H-imidazol-5-ylmethyl]-piperazin-2-one

5(S)-(2-[2,2,2-trifluoroethoxy]ethyl)-1-(3-trifluoromethylphenyl)- 4-[1-(4-cyanobenzyl)-4-imidazolylmethyl]-piperazin-2-one

1-(5,6,7,8-tetrahydronaphthyl)-4-[1-(4-cyanobenzyl)-1H-imidazol-5-ylmethyl]-piperazin-2-one

1-(2-methyl-3-chlorophenyl)-4-[1-(4-cyanobenzyl)-4-imidazolylmethyl)]-piperazin-2-one

2(RS)-{[1-(Naphth-2-ylmethyl)-1H-imidazol-5-yl)] acetyl}amino-3-(t-butoxycarbonyl)amino- N-(2-methylbenzyl) propionamide

N-{1-(4-Cyanobenzyl)-1H-imidazol-5-ylmethyl}-4(R)-benzyloxy-2(S)-{N'-acetyl-N'-3-chlorobenzyl}aminomethylpyrrolidine

N-{1-(4-Cyanobenzyl)-1H-imidazol-5-ylethyl}-4(R)-benzyloxy-2(S)-{N'-acetyl-N'-3-chlorobenzyl}aminomethyl pyrrolidine

1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl] pyrrolidin-2(S)-ylmethyl]-(N-2-methylbenzyl)-glycine N'-(3-chlorophenylmethyl) amide

1-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl] pyrrolidin-2(S)-ylmethyl]-(N-2-methylbenzyl)-glycine N'-methyl-N'-(3-chlorophenylmethyl) amide

(S)-2-[(1-(4-Cyanobenzyl)-5-imidazolylmethyl)amino]-*N*-(benzyloxycarbonyl)-*N*-(3-chlorobenzyl)-4-(methanesulfonyl)butanamine

1-(3,5-Dichlorobenzenesulfonyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

N-{[1-(4-Cyanobenzyl)-1H-imidazol-5-yl]methyl}-4-(3-methylphenyl)-4-hydroxy piperidine,

N-{[1-(4-Cyanobenzyl)-1H-imidazol-5-yl]methyl}-4-(3-chlorophenyl)-4 hydroxy piperidine,

4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-(2,3-dimethylphenyl)-piperazine-2,3-dione

1-(2-(3-Trifluoromethoxyphenyl)-pyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole

4-{5-[1-(3-Chloro-phenyl)-2-oxo-1,2-dihydro-pyridin-4-ylmethyl]-imidazol-1-ylmethyl}-2-methoxy-benzonitrile

3(R)-3-[1-(4-Cyanobenzyl)imidazol-5-yl-ethylamino]-5-phenyl-1-(2,2,2-trifluoroethyl)-H-benzo[e][1,4] diazepine

3(S)-3-[1-(4-Cyanobenzyl) imidazol-5-yl]-ethylamino]-5-phenyl-1-(2,2,2-trifluoroethyl)-H-benzo[e][1,4] diazepine

N-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine

N-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine methyl ester

N-[1-(1H-Imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine

N-[1-(1H-Imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine methyl ester

2(S)-(4-Acetamido-1-butyl)-1-[2(R)-amino-3-mercaptopropyl]-4-(1-naphthoyl)piperazine

2(RS)-{[1-(Naphth-2-ylmethyl)-1H-imidazol-5-yl)] acetyl}amino-3-(t-butoxycarbonyl)amino- N-cyclohexyl-propionamide

1-{2(R,S)-[1-(4-cyanobenzyl)-1H-imidazol-5-yl]propanoyl}-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine

1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(diphenylmethyl)piperazine

1-(Diphenylmethyl)-3(S)-[N-(1-(4-cyanobenzyl)-2-methyl-1H-imidazol-5-ylethyl)-N-(acetyl)aminomethyl] piperidine

N-[1-(1H-Imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-chlorobenzyl)glycyl-methionine

N-[1-(1H-Imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-chlorobenzyl)glycyl-methionine methyl ester

3(R)-3-[1-(4-Cyanobenzyl)imidazol-5-yl-methylamino]-5-phenyl-1-(2,2,2-trifluoroethyl)-H-benzo[e][1,4] diazepine

1-(3-trifluoromethoxyphenyl)-4-[1-(4-cyanobenzyl)imidazolylmethyl]-2-piperazinone

1-(2,5-dimethylphenyl)-4-[1-(4-cyanobenzyl)imidazolylmethyl]-2-piperazinone

1-(3-methylphenyl)-4-[1-(4-cyanobenzyl)imidazolylmethyl]-2-piperazinone

1-(3-iodophenyl)-4-[1-(4-cyanobenzyl)imidazolylmethyl]-2-piperazinone

1-(3-chlorophenyl)-4-[1-(4-cyano-3-methoxybenzyl)imidazolylmethyl]-2-piperazinone

1-(3-trifluoromethoxyphenyl)-4-[1-(4-cyano-3-methoxybenzyl)imidazolyl methyl]-2-piperazinone

4-[((1-(4-cyanobenzyl)-5-imidazolyl)methyl)amino]benzophenone

1-(1-{[3-(4-cyano-benzyl)-3*H*-imidazol-4-yl]-acetyl}-pyrrolidin-2(S)-ylmethyl)-3(S)-ethyl-pyrrolidine-2(S)-carboxylic acid 3-chloro-benzylamide

or the pharmaceutically acceptable salt thereof.

27. A method of treating cancer which comprises administering to a mammal in need thereof a pharmaceutically effective amount of a compound, which is characterized by:

a) inhibition of greater than (>) 25% of the cellular processing of a newly synthesized protein that is a substrate of one or both of geranylgeranyl-protein transferase Type I and farnesyl-protein transferase after incubation of cells in the presence of the compound; and

b) an IC_{50} (a measurement of *in vitro* inhibitory activity) of less than about 1 μM against transfer of a farnesyl residue to a protein or peptide substrate comprising a $CAAX^F$ motif by farnesyl-protein transferase.

28. The method according to Claim 27 wherein the compound inhibits greater than 50% of the cellular processing of a newly synthesized protein that is a substrate of one or both of geranylgeranyl-protein transferase Type I and farnesyl-protein transferase.

29. The method according to Claim 27 wherein the newly synthesized protein in characteristic a) is a substrate of both geranylgeranyl-protein transferase Type I and farnesyl-protein transferase.

30. The method according to Claim 27 wherein the compound inhibits transfer of a farnesyl residue to a protein or peptide substrate comprising a $CAAX^F$ motif by farnesyl-protein transferase at an IC_{50} of less than about 100 nM.

31. The method according to Claim 27 wherein the newly synthesized protein is selected from K4B-Ras and Rap1.

32. The method according to Claim 27 wherein the cells are selected from PSN-1 cells and K-*ras*-transformed Rat1 cells.

33. A method of treating cancer which comprises administering to a mammal in need thereof a pharmaceutically effective amount of a compound, which is characterized by:

a) inhibition of greater than (>) 25% of the cellular processing of a newly synthesized protein that is a substrate of one or both of geranylgeranyl-protein transferase Type I and farnesyl-protein transferase after incubation of cells in the presence of the compound;

b) an IC_{50} (a measurement of *in vitro* inhibitory activity) of less than about 1 μM against transfer of a farnesyl residue to a protein or peptide substrate comprising a $CAAX^F$ motif by farnesyl-protein transferase; and

c) an IC_{50} (a measurement of *in vitro* inhibitory activity) of less than about 5 μM against transfer of a geranylgeranyl residue to a protein or peptide substrate comprising a $CAAX^G$ motif by geranylgeranyl-protein transferase type I in the presence of a modulating anion.

34. The method according to Claim 33 wherein the compound inhibits greater than 50% of the cellular processing of a newly synthesized protein that is a substrate of one or both of geranylgeranyl-protein transferase Type I and farnesyl-protein transferase.

35. The method according to Claim 33 wherein the newly synthesized protein in characteristic a) is a substrate of both

geranylgeranyl-protein transferase Type I and farnesyl-protein transferase.

36. The method according to Claim 33 wherein the compound inhibits transfer of a farnesyl residue to a protein or peptide substrate comprising a $CAAX^F$ motif by farnesyl-protein transferase at an IC_{50} of less than about 100 nM.

37. The method according to Claim 33 wherein the compound inhibits transfer of a geranylgeranyl residue to a protein or peptide substrate comprising a $CAAX^G$ motif by geranylgeranyl-protein transferase type I in the presence of an anion at an IC_{50} of less than about 1 μM.

38. The method according to Claim 33 wherein the newly synthesized protein is selected from K4B-Ras and Rap1.

39. The method according to Claim 33 wherein the cells are selected from PSN-1 cells and K-*ras*-transformed Rat1 cells.

40. The method according to Claim 33 wherein the modulating anion is selected from: adenosine 5'-triphosphate, 2'-deoxyadenosine 5'-triphosphate, 2'-deoxycytosine 5'-triphosphate, β-glycerol phosphate, pyrophosphate, guanosine 5'-triphosphate, 2'-deoxyguanosine 5'-triphosphate, uridine 5'-triphosphate, dithiophosphate, thymidine 5'-triphosphate, tripolyphosphate, D-myo-inositol 1,4,5-triphosphate and sulfate.

41. The method according to Claim 40 wherein the modulating anion is selected from: adenosine 5'-triphosphate (ATP), β-glycerol phosphate, pyrophosphate, dithiophosphate and sulfate.

42. An assay for identifying a compound which is efficacious *in vivo* as an inhibitor of cancer cell growth, comprising the steps of:

a) incubating test cells in the presence of a test compound in an incubation medium;

b) isolating a protein that is a substrate of one or both of geranylgeranyl-protein transferase Type I and farnesyl-protein transferase; and

c) measuring the amount of the protein that has been processed and the amount of protein that has not been processed.

43. The assay according to Claim 42 wherein the protein that is a substrate of one or both of geranylgeranyl-protein transferase Type I and farnesyl-protein transferase is selected from K4B-Ras and Rap1.

44. The assay according to Claim 42 wherein the protein in step b) is a substrate of both geranylgeranyl-protein transferase Type I and farnesyl-protein transferase.

45. The assay according to Claim 42 wherein the protein that is a substrate of one or both of geranylgeranyl-protein transferase Type I and farnesyl-protein transferase is K4B-Ras.

46. The assay according to Claim 42 wherein the step of isolating the proteins comprises the additional steps of lysing the cells and then immunoprecipitating the proteins from the lysate.

47. The assay according to Claim 45 wherein the supernatant from the lysate is immunoprecipitated twice.

48. The assay according to Claim 45 wherein the step of isolating the proteins comprises the additional steps of lysing the cells and then immunoprecipitating the proteins from the lysate.

49. The assay according to Claim 48 wherein the supernatant from the lysate is immunoprecipitated twice.

50. The assay according to Claim 49 wherein the supernatant from the lysate is immunoprecipitated with pan Ras monoclonal antibody and the protein mixture obtained from the first precipitation is immunoprecipitated with K-Ras specific monoclonal antibody.

51. The assay according to Claim 42 wherein the test cells are selected from PSN-1 cells and K-*ras*-transformed Rat1 cells.

52. The assay according to Claim 42 wherein the protein of step b) is radiolabelled by introducing radiolabeled amino acids to the incubation medium.

53. The assay according to Claim 42 wherein the protein of step b) is radiolabelled by introducing a radiolabeled amino acid, that is selected from one or both of S^{35} radiolabeled methionine and S^{35} radiolabeled cysteine, to the incubation medium.

54. An assay for identifying a compound which is efficacious *in vivo* as an inhibitor of cancer cell growth, comprising the steps of:

a) incubating test cells in the presence of a test compound in an incubation medium;
b) isolating a protein that is a substrate of one or both of geranylgeranyl-protein transferase Type I and farnesyl-protein transferase; and
c) measuring the amount of the protein that has not been processed.

55. The assay according to Claim 54 wherein the protein in step b) is a substrate of geranylgeranyl-protein transferase Type I.

56. The assay according to Claim 55 wherein the protein that is a substrate of geranylgeranyl-protein transferase Type I is Rap1.

57. The assay according to Claim 54 wherein the step of isolating the proteins comprises the additional steps of lysing the cells and then separating cellular proteins by electrophoresis.

58. The assay according to Claim 57 wherein the step of isolating the proteins comprises the additional steps of performing a Western blot on the electrophoretic gel using an antibody specific for the unprocessed protein.

59. The assay according to Claim 58 wherein the antibody specific for the unprocessed protein is anti-Rap1A antibody (Santa Cruz Biochemical SC1482).

60. A method of inhibiting prenyl-protein transferases which comprises administering to a mammal in need thereof a pharmaceutically effective amount of a compound, which is characterized by:

a) inhibition of greater than (>) 25% of the cellular processing of a newly synthesized protein that is a substrate of one or both of geranylgeranyl-protein transferase Type I and farnesyl-protein transferase after incubation of cells in the presence of the compound as determined by the assay according to Claim 53; and
b) an IC_{50} (a measurement of *in vitro* inhibitory activity) of less than about 1 μM against transfer of a farnesyl residue to a protein or peptide substrate comprising a $CAAX^F$ motif by farnesyl-protein transferase.

61. A method of inhibiting farnesyl-protein transferase and geranylgeranyl-protein transferase type I which comprises

administering to a mammal in need thereof a pharmaceutically effective amount of a compound, which is characterized by:

a) inhibition of greater than (>) 25% of the cellular processing of a newly synthesized protein that is a substrate of one or both of geranylgeranyl-protein transferase Type I and farnesyl-protein transferase Type I after incubation of cells in the presence of the compound as determined by the assay according to Claim 53;

b) an IC_{50} (a measurement of *in vitro* inhibitory activity) of less than about 1 μM against transfer of a farnesyl residue to a protein or peptide substrate comprising a $CAAX^F$ motif by farnesyl-protein transferase; and

c) an IC_{50} (a measurement of *in vitro* inhibitory activity) of less than about 5 μM against transfer of a geranylgeranyl residue to a protein or peptide substrate comprising a $CAAX^G$ motif by geranylgeranyl-protein transferase type I in the presence of a modulating anion.

62. A method of treating cancer which comprises administering to a mammal in need thereof a pharmaceutically effective amount of a compound, which is characterized by:

a) inhibition of greater than (>) 25% of the cellular processing of a newly synthesized protein that is a substrate of one or both of geranylgeranyl-protein transferase Type I and farnesyl-protein transferase after incubation of cells in the presence of the compound as determined by the assay according to Claim 53;

b) an IC_{50} (a measurement of *in vitro* inhibitory activity) of less than about 1 μM against transfer of a farnesyl residue to a protein or peptide substrate comprising a $CAAX^F$ motif by farnesyl-protein transferase; and

c) an IC_{50} (a measurement of *in vitro* inhibitory activity) of less than about 5 μM against transfer of a geranylgeranyl residue to a protein or peptide substrate comprising a $CAAX^G$ motif by geranylgeranyl-protein transferase type I in the presence of a modulating anion.

63. A method for identifying a prenyl-protein transferase inhibitor which is efficacious *in vivo* as an inhibitor of geranylgeranyl-protein transferase which comprises evaluating a test compound in the assay according to Claim 53; and

a) assessing a test compound for its *in vitro* inhibitory activity against transfer of a geranylgeranyl residue to a protein or peptide substrate comprising a $CAAX^G$ motif by geranylgeranyl-protein transferase type I in the presence of a modulating anion.

64. A method for identifying a prenyl-protein transferase inhibitor which is efficacious *in vivo* as an inhibitor of geranylgeranyl-protein transferase which comprises evaluating a test compound in the assay according to Claim 53; and

a) assessing a test compound for its *in vitro* inhibitory activity against transfer of a farnesyl residue to a protein or peptide substrate comprising a $CAAX^F$ motif by farnesyl-protein transferase.

65. A method for identifying a prenyl-protein transferase inhibitor which is efficacious *in vivo* as an inhibitor of geranylgeranyl-protein transferase which comprises evaluating a test compound in the assay according to Claim 53; and

a) assessing a test compound for its *in vitro* inhibitory activity against transfer of a farnesyl residue to a protein or peptide substrate comprising a $CAAX^F$ motif by farnesyl-protein transferase.

66. A method for identifying a compound which is an inhibitor of geranylgeranyl-protein transferase type I and farnesyl-protein transferase, and which is efficacious *in vivo* as an inhibitor of the growth of cancer cells characterized by a mutated K-RasB protein, which comprises evaluating a test compound in the assay according to Claim 53; and

a) assessing a test compound for its *in vitro* inhibitory activity against transfer of a geranylgeranyl residue to a protein or peptide substrate comprising a $CAAX^G$ motif by geranylgeranyl-protein transferase in the presence of a modulating anion;

b) assessing a test compound for its *in vitro* inhibitory activity against transfer of a farnesyl residue to a protein or peptide substrate comprising a $CAAX^F$ motif by farnesyl-protein transferase.

67. The method according to Claim 66 wherein the protein is selected from K4B-Ras and Rap1.

68. The method according to Claim 66 wherein the protein that is a substrate of geranylgeranyl-protein transferase Type I is K4B-Ras.

69. The method according to Claim 66 wherein the step of isolating the proteins comprises the additional steps of lysing the cells and then immunoprecipitating the proteins from the lysate.

70. The method according to Claim 67 wherein the supernatant from the lysate is immunoprecipitated twice.

71. The method according to Claim 67 wherein the step of isolating the proteins comprises the additional steps of lysing the cells and then immunoprecipitating the proteins from the lysate.

72. The method according to Claim 71 wherein the supernatant from the lysate is immunoprecipitated twice.

73. The method according to Claim 71 wherein the supernatant from the lysate is immunoprecipitated with pan Ras monoclonal antibody and the protein mixture obtained from the first

precipitation is immunoprecipitated with K-Ras specific monoclonal antibody.

74. The method according to Claim 73 wherein the test cells are selected from PSN-1 cells and K-*ras*-transformed Rat1 cells.

75. A method for identifying a compound which is an inhibitor of geranylgeranyl-protein transferase type I and farnesyl-protein transferase, and which is efficacious *in vivo* as an inhibitor of the growth of cancer cells characterized by a mutated K-RasB protein, which comprises evaluating a test compound in the assay according to Claim 53; and

a) assessing a test compound for its *in vitro* inhibitory activity against transfer of a farnesyl residue to a protein or peptide substrate comprising a $CAAX^F$ motif by farnesyl-protein transferase.

76. A method for identifying a compound which is an inhibitor of geranylgeranyl-protein transferase type I and farnesyl-protein transferase, and which is efficacious *in vivo* as an inhibitor of the growth of cancer cells characterized by a mutated K-RasB protein, which comprises evaluating a test compound in the assay according to Claim 59; and

a) assessing a test compound for its *in vitro* inhibitory activity against transfer of a farnesyl residue to a protein or peptide substrate comprising a $CAAX^F$ motif by farnesyl-protein transferase.

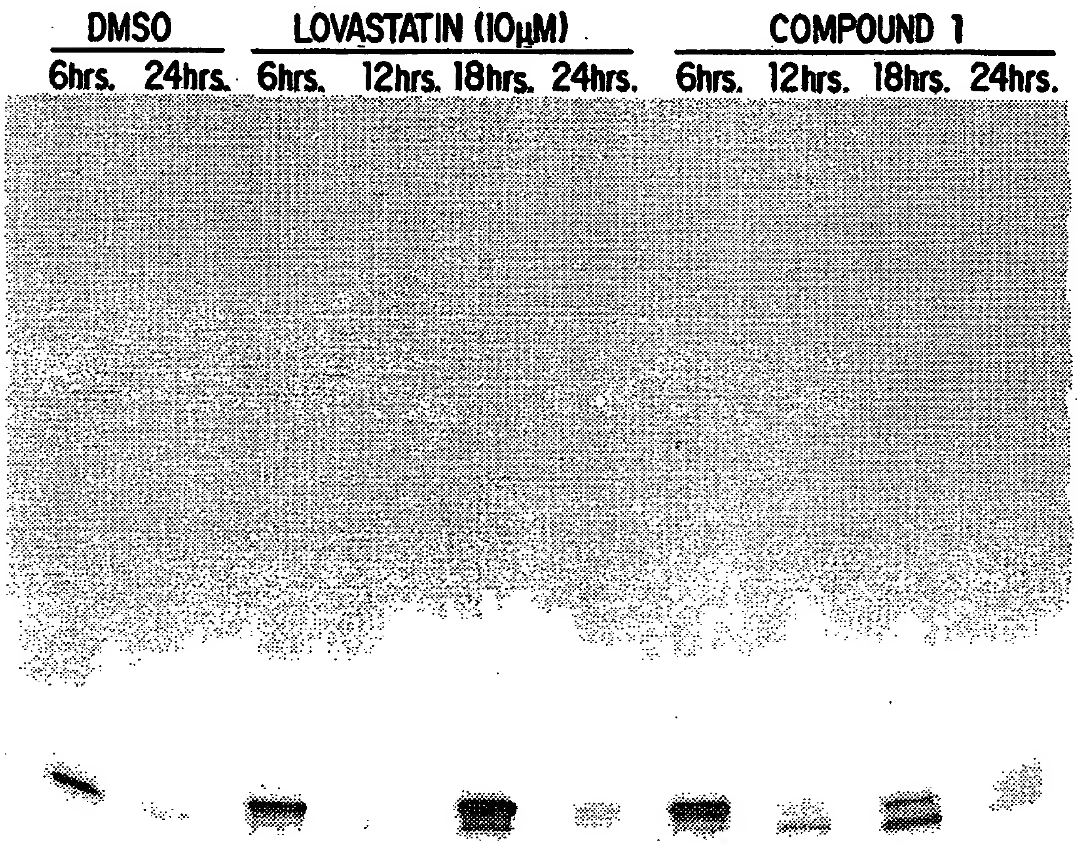

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FIG.1

SEQUENCE LISTING

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Anne E. Burkhardt
Pearl S. Huang
Kenneth S. Koblan
Nancy E. Kohl
Robert B. Lobell
Carolyn A. Buser-Doepner

<120> A METHOD OF TREATING CANCER

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/17698

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X - A	Chemical Abstract, Volume 126, abstract No. 8133, ANTHONY et al, "Preparation of Piperazine and Homopiperazine Inhibitors of Farnesyl-Protein Transferase", WO 9630343 A1, abstract, 03 October 1996, see entire abstract.	1-41, 60-62 ---- 42-59, 63-76
A	US 5,185,248 A (BARBACID et al) 09 February 1993, see the entire document.	1-76

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
"B" earlier document published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search
19 NOVEMBER 1998

Date of mailing of the international search report
22 DEC 1998

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For
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/17698

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

C12Q 1/48; C12N 9/10; A01N 43/00, 43/40, 43/50; A61K 31/55, 31/415, 31/445

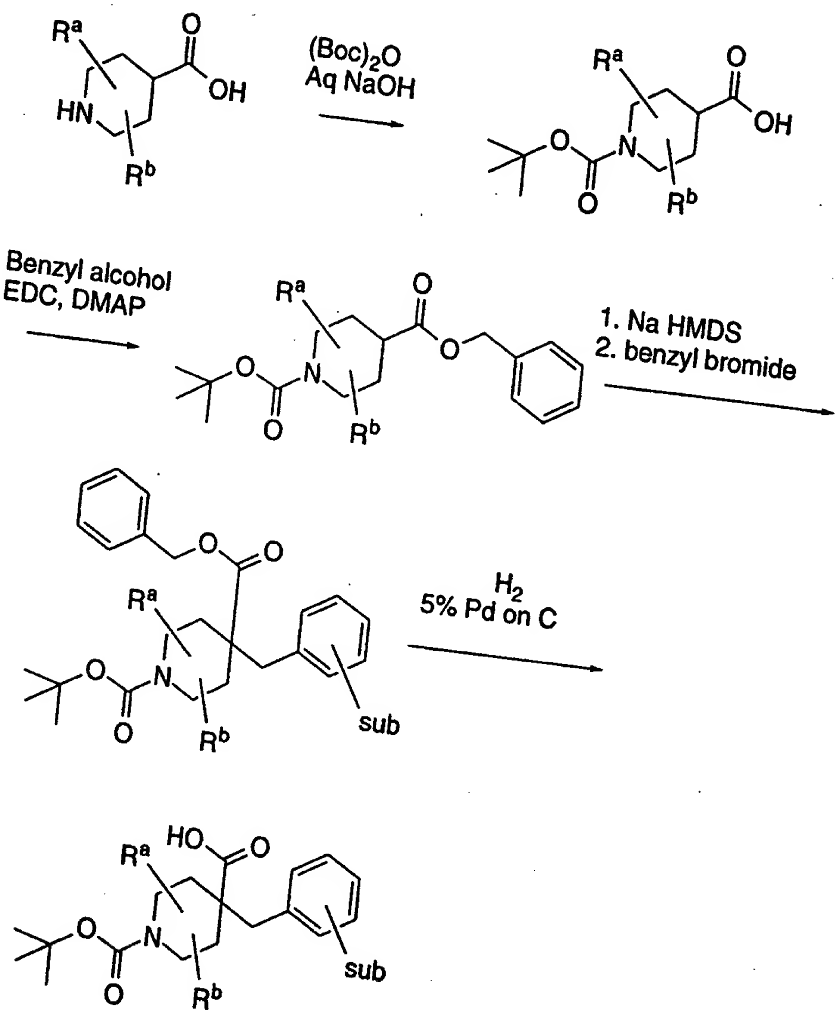
A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

435/7.2, 7.37, 7.72, 15, 29, 172.3, 193; 514/211, 315, 326, 327, 330, 331, 345, 350, 351, 354, 357, 396, 397, 398, 399, 400

B. FIELDS SEARCHED
Minimum documentation searched
Classification System: U.S.

435/7.2, 7.37, 7.72, 15, 29, 172.3, 193; 514/211, 315, 326, 327, 330, 331, 345, 350, 351, 354, 357, 396, 397, 398, 399, 400

SCHEME 29



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